Welcome to Current Clinical Challenges: Managing Type 2 Diabetes.
Current Clinical Challenges: Managing Type 2 Diabetes

- This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME®) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and Excellence in Medical Education. PIM is accredited by the ACCME to provide continuing medical education for physicians.

- This activity is supported by an educational grant from Novo Nordisk

This interactive CME case study program is jointly sponsored by Excellence in Medical Education and The Postgraduate Institute for Medicine.

Educational support for this program has been provided by Novo Nordisk.
You will have an opportunity during the program to answer embedded interactive questions.

After viewing the fully synchronized slide and audio presentation, you will have the opportunity to submit a post-test and evaluation form in order to receive CME credit.

While viewing the presentation, you can control the slides and audio by using the PLAY, PAUSE, NEXT and PREVIOUS controls. You can also jump to a specific slide using the thumbnail images at the bottom of your screen. You can zoom into the slides by clicking the ENLARGE SLIDE button then click the slide again to return it to its normal size.
The faculty for this program is Dr. Ramachandiran Cooppan. Dr. Cooppan is an Assistant Clinical Professor of Medicine at Harvard Medical School, in Boston, Massachusetts. He also is a senior staff physician at Joslin Diabetes Center and a senior attending physician at Beth Israel Deaconess Medical Center, both located in Boston.
Educational Objectives

After completing this activity, the participant should be better able to:

• Review the ß-cell dysfunction that occurs as a result of high secretory demands imposed by insulin resistance
• Identify the benefits of initiating insulin therapy in patients with disease progression in whom oral medications are failing
• Explain the differences between the various insulins available and their pharmacodynamic properties
• Explain a protocol for insulin initiation and titration in type 2 diabetes
• Discuss appropriate management strategies in patients developing diabetes-related complications

And now, I would like to turn the program over to Dr. Cooppan.
Diabetes Mellitus

- Affects approximately 20.8 million people (7% of US population)
  - Majority are adults (≥20 years of age)
    - ~50% are ≥60 years of age
  - 14.6 million have received a diagnosis
    - Type 1 DM (5% to 10% of diagnosed cases)
    - Type 2 DM (90% to 95% of diagnosed cases)
    - Gestational (20% to 50% chance of developing diabetes within the next 5-10 years)
    - Other (1% to 5% of diagnosed cases)

Diabetes mellitus affects approximately 20.8 million people in the United States roughly 7% of the US population.1
- About 176,500 individuals <20 years of age have diabetes mellitus (DM) (types 1 and 2)
- Majority are adults (≥20 years of age); ~50% are ≥60 years of age
- Of the 20.8 million individuals with DM
  - 14.6 million have received a diagnosis of DM
  - 6.2 million remain undiagnosed

4 Major Classes of DM
- Type 1
  - Accounts for 5% to 10% of all diagnosed cases of DM
- Type 2
  - Accounts for 90% to 95% of all diagnosed cases of DM
- Gestational
  - Approximately 5% to 10% of women with gestational DM have type 2 DM after pregnancy
    - Women who have gestational DM have a 20% to 50% chance of developing DM 5–10 years after pregnancy
- Other
  - Etiologies include surgery, drugs, malnutrition, infection, other illnesses
  - Some classify latent autoimmune diabetes in adults (LADA) within this group2
  - Accounts for about 1% to 5% of all diagnosed cases of DM

Prediabetes

- Impaired glucose tolerance (IGT)
  - 2-hour glucose
    - 140–200 mg/dL
- Impaired fasting glucose (IFG)
  - Fasting plasma glucose (FPG) 100–125 mg/dL

Estimated total prevalence of IFG, IGT, and prediabetes in people aged 40–74 years—United States, 2000


Prediabetes

- Condition associated with increased risk of type 2 DM, cardiovascular disease, and stroke
- Characterized by the presence of impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or both
- In a cross-sectional sample of adults aged 40–74 years (tested from 1988–1994)
  - 33.8% had IFG
  - 15.4% had IGT
  - 40.1% had prediabetes (IFG or IGT or both)
- Extrapolating these results to the entire US population in 2000, it is estimated that
  - 35 million adults (aged 40–74 years) had IFG
  - 16 million adults had IGT
  - 41 million adults had prediabetes, (overlap between IFG and IGT groups)
- Recent analysis of National Health and Nutrition Examination Survey (NHANES) 1999–2000 data suggest
  - Nearly 40% of adults >65 years of age have IFG
  - IFG and undiagnosed DM are much more common in men than in women
- Data suggest that progression to frank DM is not inevitable in this group of patients
  - Lifestyle modifications can prevent or delay DM

Prevalence of DM in US Adults ≥20 Years of Age

- 20.6 million individuals ≥20 years of age have DM
  - 50% of those individuals are ≥60 years of age
- Men: 10.9 million men (≈10.5%) ≥20 years of age have DM
- Women: 9.7 million women (≈8.8%) ≥20 years of age have DM
- Review of NHANES revealed that prevalence of diagnosed DM in 2002 was 6.5% of adults ≥20 years of age
  - Prevalence of undiagnosed diabetes was 2.8%

Prevalence by Ethnicity in Adults ≥20 Years of Age

- Prevalence of DM is higher in Native Americans, African Americans, Hispanic Americans, and Asian Americans and Pacific Islanders than in non-Hispanic white individuals
  - Native Americans: 99,500 individuals have diagnosed diabetes; after applying the rate of undiagnosed diabetes in the total US population to Native Americans, an estimated 118,000 individuals (15.1% of US Native American/Alaskan Native population) have diabetes
  - Total prevalence is lowest in Alaskan Natives and greatest in Native Americans in the south/southwest
  - African Americans (non-Hispanic blacks): 3.2 million individuals (13.3% of US African American population)
    - More prevalent in women and in those >65 years of age
    - Gestational DM is 50% to 80% more common in African American women than in white women
  - Hispanic Americans: 2.5 million (9.5% of US Hispanic American population)
    - Largest subgroup: Mexican Americans
  - Asian Americans and Pacific Islanders: total prevalence not available

Adolescents

- Current data suggest that type 2 DM in young people (<20 years of age) is being diagnosed more frequently, particularly among Hispanic Americans, followed by non-Hispanic black and non-Hispanic white adolescents

Incidence of DM—United States, 2005

- Approximately 1.5 million new cases of DM were diagnosed among people ≥20 years of age in 2005

- Interestingly, the incidence of type 2 DM may be similar among the “at-risk” ethnic groups
  - In the Diabetes Prevention Program cohort of 3234 individuals with IGT and IFG, similar rates of DM development (approximately 11 cases per 100 persons per year) were seen across racial and ethnic groups
    - These results suggest that once an individual exhibits IGT or IFG, the risk of progression is the same regardless of ethnic group; whatever factors predispose an individual group to the development of DM, the maximal effects of ethnic or genetic factors are exerted during the transition from normal glucose tolerance to IGT and/or IFG


Goals for Glycemic Control

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<tr>
<th>Measurement</th>
<th>ADA</th>
<th>AACE/ACE</th>
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<td>A1c, %</td>
<td>&lt;7.0</td>
<td>≤6.5</td>
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<td>Fasting/preprandial glucose, mg/dL</td>
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<td>&lt;110</td>
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<tr>
<td>2-hour postprandial glucose (PPG), mg/dL</td>
<td>&lt;180</td>
<td>&lt;140</td>
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</tbody>
</table>

A1c = hemoglobin A1c; ADA = American Diabetes Association; AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology.


- Several professional associations have developed guidelines for the prevention, classification, diagnosis, and management of DM
  - Recommended goals for glycemic control are shown¹,²
- Data suggest that target goals for glucose control are not being met in many patients with type 2 DM
    - NHANES III: 44.5% of those with type 2 DM had A1c <7%
    - NHANES 1990–2000: 35.8% of those with type 2 DM had A1c <7%
  - American Association of Clinical Endocrinologists study (2003–2004): 67% of Americans with type 2 DM failed to meet target (A1c ≤6.5%)⁴
  - Studies have also shown that pharmacotherapy is frequently started late and that doses are not titrated adequately⁵
  - Other reasons for failure of therapy may include⁵
    - Financial constraints
    - Reluctance of patients to use insulin (or other therapies)
    - Lack of conviction by healthcare professionals (and third-party payers) that DM treatment is effective and beneficial

• This slide illustrates the types of treatment used in patients with DM in the United States (2001–2003 data)
  – Patients with type 1 diabetes are treated with insulin only
  – Patients with type 2 diabetes may be treated using nonpharmacologic strategies (eg, self–blood glucose monitoring [SMBG], lifestyle modifications, and DM self-management education; oral medications; insulin; or all 3 methods
  – “Neither” includes those using only nonpharmacologic treatment strategies to control blood glucose levels
• The statistics shown here are consistent with the fact that type 2 DM (treated with oral agents, at least initially) is the most common type of DM

The economic burden imposed by DM on society and the individual is substantial.  
- 2002 estimates of medical expenditures in the United States
  - Total (direct and indirect): $132 billion
  - Direct medical costs: $92 billion
  - Indirect costs: $40 billion (eg, disability, work loss, premature death)
  - Based on 2002 data, the annual cost of treating DM could be as high as $156 billion by 2010 and $192 billion by 2020.

Improved glycemic control is associated with economic and quality-of-life (QOL) benefits.
- Economic benefits include retained employment, greater productivity, reduced absenteeism, and reduced number of days of restricted activity
- Intensive control may be associated with higher treatment costs but is associated with substantial reductions in the cost of treating complications of DM
  - Supported by data from United Kingdom Prospective Diabetes Study (UKPDS) and Centers for Disease Control and Prevention (CDC) Cost-effectiveness Study

CDC Cost-effectiveness Study (2002)
- Evaluated a hypothetic cohort of adults (>25 years of age) with newly diagnosed type 2 DM
- Incremental cost-effectiveness ratio (ICER) for intensive glycemic control was $41,384 per quality-adjusted life-year (QALY) gained
  - In the United States, <$50,000 per QALY is generally considered an acceptable ICER.
  - Comparable with other adopted healthcare interventions (eg, hypertension screening and therapy vs no screening among asymptomatic 20-year-old men)

References:
4. CDC Cost-effectiveness Study (2002)
5. Ubel PA. What is the price of life and why doesn’t it increase at the rate of inflation? Arch Intern Med. 2003;163:1637-1641.
Quality-of-life Issues

- Quality of life (QOL) affected by disease and treatment
- Statistically and clinically significant correlates of decreased overall QOL in patients with type 2 diabetes
  - Symptomatic microvascular complications
  - Heart failure
  - Number of medications
  - Depression
    - Depression was the strongest correlate

Both the complications of DM and the burden of treatment contribute to decline of health-related QOL in patients with DM

A recent study assessed the effect of medical comorbidities, depression, and treatment intensity on QOL in 909 patients with type 2 DM

- 35% had coronary heart disease (CHD); 49% had microvascular complications; 13% had depression
- In univariate analyses, CHD, stroke, microvascular complications, heart failure, chronic obstructive pulmonary disease, and depression were all associated with reduced QOL
  - Patients with depression had the lowest health-related QOL
  - No reduction in QOL was associated with hypertension, dyslipidemia, obesity, or smoking
  - Greater numbers of medications, insulin use, and longer duration of DM were associated with decreased QOL
- In final multivariable analyses, after adjusting data for age, sex, and socioeconomic differences, among other factors, complications found to be statistically and clinically significant correlates of decreased overall QOL were
  - Symptomatic microvascular complications
  - Heart failure
  - Number of medications
  - Depression
    - Depression was the strongest correlate with decreased QOL

Studies have shown that prevalence of depression is higher in those with DM than in those without
- Associated with increased healthcare costs

Case Study: J. M.

- 55-year-old Latina woman
- Increased urination, thirst, and fatigue and a 4-lb weight loss
- Infrequent self-monitoring of blood glucose (SMBG)
  - Fasting blood glucose (FBG): 160–200 mg/dL
  - Preprandial: 150–170 mg/dL
- Current treatment (Rx)
  - Glimepiride 2 mg daily
  - Metformin 1000 mg twice daily
- Other medical problems
  - Hypertension (Rx—lisinopril)
  - Dyslipidemia (Rx—fenofibrate, atorvastatin)

- J. M. is a 55-year-old Latina woman with type 2 DM, diagnosed 8 years ago
- She seeks medical attention for increased urination, thirst, fatigue, and 4-lb weight loss
- She performs SMBG infrequently
  - Fasting blood glucose (FBG) generally 160–200 mg/dL
  - Predinner glucose generally 150–170 mg/dL
- Current treatment
  - Glimepiride 2 mg daily
  - Metformin 1000 mg twice daily
  - 3 years since last saw dietician
- Other medical problems
  - Hypertension: treated with lisinopril 20 mg daily
  - Dyslipidemia: treated with fenofibrate 160 mg and atorvastatin 10 mg daily
- Pertinent family history
  - Mother: type 2 DM; died from acute myocardial infarction at age 74 years
  - Father: hypertension; died from cerebrovascular accident at age 78 years
  - Maternal uncles: 2 with type 2 DM
  - Sister: type 2 DM
- Pregnancy: para 3, gravida 3; last child 20 years previously—term (7 lb, 8 oz)
- Social history: homemaker; nonsmoker; no alcohol dependency
**J. M.—Patient Examination**

- **Physical examination**
  - Height: 64 in
  - Weight: 156 lb
  - Body mass index (BMI): 26.8 kg/m²
  - Blood pressure (BP): 130/76 mm Hg
  - Loss of monofilament in feet with reduced vibration in ankles

- **Laboratory values**
  - Random glucose: 264 mg/dL
  - A1c: 8.4%
  - Urine: negative ketones; albumin-to-creatinine ratio: 56 μg/mg (normal <30 μg/mg)

- What do the physical examination and laboratory analysis tell us about this patient?
  - J. M. is overweight, as evidenced by her body mass index (BMI) of 26.8 kg/m² (overweight = 25–29.9 kg/m²)
  - Her glucose level is significantly elevated, and her A1c is 1.4% above the American Diabetes Association (ADA) goal (<7%)
    - She exhibits signs of diabetic complications (ie, neuropathy and microalbuminuria)
  - Her hypertension is under control
  - No information about dyslipidemia control is available
JM - Question 1: What are the probable causes of worsening diabetes in this patient?

A. Increasing insulin resistance
B. Decreasing insulin secretion
C. Inadequate oral medication
D. Poor adherence to diet
E. All of the above

Pop-Up Answers to Question 1

A. Correct, likely a contributing factor, but not the only cause
Insulin resistance is the primary defect in the pathogenesis of type 2 diabetes, and the severity of insulin resistance increases as an individual moves from impaired glucose tolerance to mild type 2 diabetes. Once frank diabetes occurs, the level of insulin resistance in patients with type 2 diabetes remains relatively static.

B. Correct, likely a contributing factor, but not the only cause
The natural history of type 2 diabetes includes a progressive decline in β-cell function, ultimately resulting in an absolute insulin deficiency. Patients should be counseled that most individuals with type 2 DM eventually require insulin.

C. Correct, likely a contributing factor, but not the only cause
Sulfonylureas such as glimepiride are effective early on in the disease, but their ability to promote insulin secretion diminishes as β-cell function continues to decline. The secondary failure rate of sulfonylureas is approximately 5%-10% per year. Although it does not halt β-cell function decline, the use of metformin may delay the onset of secondary failure. This may be related to its effect in improving insulin sensitivity.

D. Correct, likely a contributing factor, but not the only cause
Medical nutrition therapy is an important part of the care of patients with diabetes. An individualized nutrition plan should be developed by a registered dietician, and should take into account cultural, lifestyle, and financial considerations. If disease monitoring reveals that glycemic control and nutrition-related outcomes are not being met (as in this patient), changes must be made in the patient’s treatment plan.

E. Absolutely correct!
A combination of all of the above.
Type 2 DM is characterized by insulin resistance, impaired insulin secretion, and abnormal hepatic glucose metabolism (as measured indirectly via splanchnic glucose uptake)

- Absolute cause of metabolic defects is unknown

**Insulin Resistance Is Primary Metabolic Defect**

- Initially, β cells compensate for insulin resistance by producing more insulin, resulting in hyperinsulinemia
  - Compensatory mechanism may be adequate for up to several years
  - Eventually, IGT and mild postprandial hyperglycemia become evident
- Insulin resistance worsens → continued global defects in insulin secretion result in increased hepatic glucose production and development of impaired fasting glucose (IFG)
  - Insulin resistance also contributes to dyslipidemia, hypertension, and increased risk for cardiovascular disease

**Progression From IGT/IFG to Type 2 DM**

- Severe insulin resistance
  - Full expression of genetic abnormalities
  - Also influenced by obesity, aging, and decreased physical activity
- Continued decline in β-cell function (and insulin secretion) to the point where compensation for insulin resistance is impossible

**β-Cell Function Determines Onset of Frank DM and Progression of Disease**

- β cell becomes refractory to glucose → relative insulin deficiency develops → hyperglycemia worsens to the point of frank DM
- As insulin production decreases and insulin levels drop, insulin’s inhibitory effect on hepatic glucose production is lost
- β-cell function continues to decline until significant insulin deficiency develops
  - No longer responsive to secretagogues

## Type 2 Diabetes

### Risk Factors

- Age >45 years
- BMI >25 kg/m²
- Family history of diabetes
- Physical inactivity
- Race/ethnicity
- Previously identified IGT/IFG
- History of gestational diabetes
- BP >140/90 mm Hg
- HDL-C <35 mg/dL or TG >250 mg/dL
- Polycystic ovary disease
- History of vascular disease

HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.


### Risk include

- Older age
- Obesity
- Family history
  - ≈60% of children of diabetic parents have abnormal glucose tolerance by age 60 years
- History of gestational DM
- Physical inactivity
- Race/ethnicity
  - Type 2 DM is a complex disorder associated with variants or mutations of multiple genes
    - Frequency varies among ethnic groups
  - Highest prevalence rates of type 2 DM
    - African Americans, Asian Americans and Pacific Islanders, Hispanic Americans, Native Americans
- Presence of metabolic syndrome (≥3 features) significantly increases risk for type 2 DM
  - Abdominal obesity
  - High serum triglyceride (TG) levels
  - Low levels of high-density lipoprotein cholesterol (HDL-C)
  - Hypertension
  - IFG


JM – QUESTION 2: What should the next step be after discussing goals of treatment with this patient?

A. Send to a dietician for review of meal plan
B. Increase SMBG to include 2-hour postprandial tests
C. Increase glimepiride to 4 mg daily
D. Add a thiazolidinedione (TZD)
E. Add basal insulin

Pop-Up Answers to Question 2

A. **Possible choice** – Medical nutrition therapy is an important part of the care of patients with diabetes. An individualized nutrition plan should be developed by a registered dietician, and should take into account cultural, lifestyle, and financial considerations. If disease monitoring reveals that glycemic control and nutrition-related outcomes are not being met (as in this patient), changes must be made in the patient’s treatment plan.


B. **Excellent choice (but not the only choice)** – Based on the patient’s reported (albeit infrequent) SMBG, we know that FBS is generally high and blood glucose appears to remain elevated throughout the day. However, we have no information about postprandial hyperglycemia. At this A1c level, FPG and PPG contribute to overall almost equally. Knowledge about the presence (or absence) of postprandial hyperglycemia may help guide modifications to JM’s therapy.


C. **Possible choice** – While it is possible that an increase in sulfonylurea might provide some benefit, it is also likely that β-cell dysfunction has progressed in this patient to a point where dosage increase will not provide any significant enhancement of insulin production/secretion.

D. **Possible choice** – Triple oral therapy targets 3 metabolic abnormalities seen in type 2 diabetes: TZDs target insulin resistance, sulfonylureas enhance insulin secretion, and metformin reduces hepatic glucose production. In clinical trials, combination therapy with glitazones, SUs, and metformin has produced durable reductions in FPG and A1c. Based on clinical trials, the case for adding a TZD as a third agent seems strongest when A1c is ≤8%. In addition, the use of TZDs can be associated with weight gain and edema – a situation which should be minimized in this overweight patient with hypertension.


E. **Possible choice** – Basal insulin would target FPG, which is definitely contributing to the overall hyperglycemia. And according to ADA recommendations, preprandial glucose is the first therapeutic target. PPG is targeted when preprandial glucose is within goal (90-130 mg/dL), but A1c is not. However, JM is already receiving 2 oral agents that also target FPG – and assuming these 2 agents still have activity in this patient, targeting FPG may not to be adequate for glycemic control especially if the patient has significant increases in postprandial glucose levels.

## Pharmacologic Therapies

<table>
<thead>
<tr>
<th>Class/Generic Name</th>
<th>Trade Name</th>
<th>Dose Range*, mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td></td>
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<tr>
<td>Glipizide</td>
<td>Glucotrol®/Glucotrol XL®</td>
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<td>Glyburide</td>
<td>Micronase®/DiaBeta®</td>
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<td>Glyburide, micronized</td>
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<td>Glimepiride</td>
<td>Amaryl®</td>
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<td><strong>Meglitinides</strong></td>
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<td><strong>Combinations</strong></td>
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<td>Glipizide + metformin</td>
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<tr>
<td>Glyburide + metformin</td>
<td>Glucovance®</td>
<td>1.25/250–20/2000</td>
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</table>

*Dose ranges obtained from individual product prescribing information.

### Secretagogues

- Both sulfonylureas and meglitinides act by blocking adenosine triphosphate–dependent potassium channels in β-cell membranes, leading to opening of calcium channels; the resulting increase in intracellular calcium induces insulin secretion

#### Sulfonylureas

- Clinically available sulfonylureas most commonly used
  - Glyburide (DiaBeta®, Sanofi-Aventis; Micronase®, Pfizer; Glynase®, Pfizer)
  - Glipizide (Glucotrol®, Pfizer)
  - Glimepiride (Amaryl®, Sanofi-Aventis)
- Concern regarding exhaustion of β-cell functioning: may be more due to natural progression of type 2 DM, independent of treatment
- Adverse effects
  - Weight gain
  - Hypoglycemia, particularly in those with renal insufficiency or irregular meals
  - Glyburide (but not glimepiride) interferes with myocardial ischemic preconditioning, which may increase risk for cardiovascular events after myocardial infarction or during angioplasty

#### Meglitinides

- Characterized by rapid onset and abbreviated duration of action
- Induce insulin release in a glucose-sensitive fashion (ie, effect diminishes with reduced glucose concentrations)
- Associated with lower risk for postabsorptive hypoglycemia and tissue exposure to hyperinsulinemia than sulfonylureas
- Available agents
  - Repaglinide (Prandin®, Novo Nordisk)
  - Nateglinide (Starlix®, Novartis)

#### Biguanides

- Inhibit hepatic gluconeogenesis directly and by enhancing the suppressive effects of insulin on hepatic glucose production
- Metformin (Glucophage®, Bristol-Myers Squibb)
- Advantages: prevention of weight gain or promotion of weight loss
- Disadvantages: gastrointestinal side effects; lactic acidosis, particularly in patients with renal insufficiency

Pharmacologic Therapies (cont’d)

<table>
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<th>Class/Generic Name</th>
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<td>Miglitol</td>
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<tr>
<td>Pioglitazone + metformin</td>
<td>Actoplus Met™</td>
<td>15/500–45/2550</td>
</tr>
</tbody>
</table>

*Dose ranges obtained from individual product prescribing information. Riddle MC. Endocrinol Metab Clin North Am. 2005;34:77-98.

**α-Glucosidase Inhibitors**
- Impair breakdown of complex sugars in the gut into glucose, slowing absorption, thus reducing postprandial glucose (PPG) excursions
- May have favorable effects on secretion of certain beneficial gut peptides (eg, glucagon-like peptide-1)
- Commercially available
  - Acarbose (Precose^®, Bayer US)
  - Miglitol (Glyset^®, Pfizer)
- Advantages: negligible/absent risk for hypoglycemia
- Disadvantages: gastrointestinal side effects (eg, flatulence) are common; acarbose has been implicated in hepatic dysfunction with chronic therapy

**Glitazones**
- Bind to peroxisome proliferator–activated receptors, reducing insulin resistance in muscle, fat, and hepatic tissue
- Advantages: useful in combination therapy; may improve secretory function of β cells; antiatherogenic effects (via modulation of inflammatory processes within the vasculature)
- Disadvantages: weight gain/fluid retention

**Dipeptidyl peptidase IV inhibitors**
- A new therapeutic class recently approved by the Food and Drug Administration

Reduction in A1c in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Reduction in A1c</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5% to 1.0%</td>
<td>α-Glucosidase inhibitors</td>
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<tr>
<td></td>
<td>Nateglinide</td>
</tr>
<tr>
<td>1.5% to 2.0%</td>
<td>Sulfonyleas, repaglinide, metformin, TZDs</td>
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</table>

- Typically observed reduction in A1c (from baseline of 8.5% to 9.0%) with different classes of oral agents as monotherapy
- In general, the greater the baseline A1c, the greater the therapeutic effect observed
- Primary improvement in overnight and preprandial glucose
  - Sulfonyleas, repaglinide, metformin, and thiazolidinediones (TZDs)
- Primary improvement in PPG excursions
  - α-Glucosidase inhibitors and nateglinide

J. M.—4 Weeks After Initial Visit

Current Rx: glimepiride 2 mg daily; metformin 1000 mg twice daily

Blood Glucose Log Showing FBG and PPG, mg/dL

<table>
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<tr>
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<th>Dinner</th>
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<td>240 pp</td>
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<td>T</td>
<td>168</td>
<td>197</td>
<td>174</td>
<td>183</td>
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<td>215 pp</td>
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<td>W</td>
<td>148</td>
<td>174</td>
<td>132</td>
<td>126</td>
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<td>196 pp</td>
<td></td>
<td>193 pp</td>
<td></td>
<td>Afternoon walk</td>
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<tr>
<td>Th</td>
<td>179</td>
<td>163</td>
<td>173</td>
<td>186</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>130 pp</td>
<td></td>
<td>Very few carbohydrates</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>with dinner</td>
</tr>
<tr>
<td>F</td>
<td>164</td>
<td>176</td>
<td>163</td>
<td>186</td>
<td></td>
</tr>
<tr>
<td></td>
<td>210 pp</td>
<td></td>
<td>243 pp</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

pp = postprandial.

The patient returns after 4 weeks. She has seen the dietician and has tried to measure 2-hour PPG levels at least once daily.

What This Glucose Log Tells You

- FBG is not under control
- High PPG after every meal, which carries over to next meal (or bedtime)
- Only time glucose was within reason was at dinner on the day she went for a walk, and at bedtime when she had few carbohydrates at dinner
Road Map to Achieve Glycemic Goals: Treated Patients (Type 2)

- This slide shows one possible approach to achieving glycemic control from the American College of Endocrinology and American Association of Clinical Endocrinologists
- It correlates increased A1c levels with current therapy and possible interventions to get to goal
- Many options are available
- A pdf version of this slide is available on the Web site noted for your reference
J. M.—Question 3

Based on the glucose log, what treatment changes would you make at this time?

A. Add TZD
B. Add basal insulin
C. Add basal insulin and stop glimepiride
D. Start insulin aspart 70/30 premix before dinner
E. Add exenatide (Byetta®) or pramlintide (Symlin®)

Please make your selection and click on the "Submit" button below.

Pop-Up Answers

A. Possible, but not best choice: Combination therapy with glitazones, SUs, and metformin produced and maintained impressive reductions in FPG and A1c throughout the duration of the trials. The addition of rosiglitazone to SUs resulted in significant improvements in insulin sensitivity and estimates of β-cell function as compared to baseline. In addition, their use is associated with weight gain – a situation which should be minimized in this overweight patient.

B. Possible, but not best choice: Basal insulin therapy is designed to mimic the constant release of endogenous insulin that regulates lipolysis and hepatic glucose output; however, given JM’s postprandial hyperglycemia, basal insulin therapy might not provide adequate glycemic control though lowering the FPG may improve PPG levels.

C. Not a good choice: Although continued β-cell failure (and unresponsiveness to the SU) is likely to be a contributing factor, it is unlikely that basal insulin alone would provide adequate glycemic control in this patient.

D. Best Choice: Data from the UKPDS revealed that less than 33% of patient treated with SUs and metformin will have A1c in the target range (<7%) within 3 years of diagnosis. Administration of premix insulin therapy prior to dinner will cover the late postprandial glucose excursion and provide glycemic control throughout the night, thus reducing FBS.

E. Good choice, but better earlier in disease: Exenatide (Byetta), an incretin mimetic, increases the release of insulin from the pancreas, decreases pancreatic glucagon release, stimulates satiety centers in the hypothalamus, and slows gastric emptying. It has also been shown to induce weight loss, reduce A1c and improve β-cell function. This injectable agent is currently indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, an SU, or both but have not achieved adequate glycemic control. The efficacy of this product depends on the individual patients residual β-cell function. The effect may be less in a patient on 2 drugs, who is 8 years into their disease. Twice daily injections and nausea can be a problem with this drug.

Pramlintide, a synthetic analog of amylin, produces many of the same therapeutic effects as exenatide. This injectable agent is currently indicated as adjunctive treatment in patients using mealtime insulin and who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin. Since JM has not tried insulin therapy, pramlintide isn’t an option.
GLP-1 Agonists

• Potentiates postprandial insulin secretion
• Inhibits glucagon secretion
• Slows gastric emptying

Glucagon-like Peptide-1 (GLP-1)
• One of 2 intestinally secreted peptides that amplify insulin response to oral delivery of glucose
• Actions of GLP-1
  – Glucose-dependent stimulation of insulin secretion by β cells (ie, negligible activity at normal or hypoglycemic glucose concentration)
  – Glucose-dependent inhibition of glucagon secretion
  – Stimulation of transcription/translation of proinsulin genes and replenishment of intracellular insulin
  – Slows gastric emptying
  – Increases sense of satiety following meals (centrally mediated)
  – Stimulation of proliferation and inhibition of apoptosis of β cells
  • Unknown whether this could be potential therapeutic effect of GLP-1 agonists

GLP-1 Agonists (incretin mimetics)
• Mechanism of action
  – Completely different site of action than sulfonylureas or meglitinides
  – Bind to GLP-1 receptor on β cells, leading to increased intracellular cyclic adenosine monophosphate, thus stimulating several intracellular signaling pathways
• Therapeutic effect: reduce fasting and PPG concentrations
  – Enhance insulin secretion in response to meals
  – Control abnormally excessive glucagon secretion seen in type 2 DM
  – Slow gastric emptying, allowing time for insulin response (slow in type 2 DM) after meals

Exenatide (Byetta®, Amylin Pharmaceuticals/Eli Lilly)
• Synthetic analog of exendin-4, which is derived from Gila monster venom
• Potent agonist of GLP-1 receptor
  – Resistant to degradation by serum enzyme, dipeptidyl peptidase IV (DPP-IV)
• Injectable agent (subcutaneous via pen injector)
• Indicated in combination with sulfonylurea and/or metformin
  – May increase risk for hypoglycemia with sulfonylurea
• Not recommended for use in patients with end-stage renal disease or gastrointestinal disorders due to high incidence of gastrointestinal adverse effects (particularly nausea)
• Pivotal clinical trial results (next slides)

Liraglutide (Novo Nordisk)
• Acylated GLP-1 analog bound to albumin (which confers resistance to DPP-IV)
• Replicates all metabolic activities of endogenous GLP-1
• In late-stage clinical trials
  – Recent data presented at June 2006 American Diabetes Association (ADA) meeting (next slides)

Incretins are a new class of antidiabetic agents recently introduced into the armamentarium of physicians.

Exenatide in Type 2 Diabetes: Clinical Trial Results at 30 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Exenatide 5 µg Twice Daily</th>
<th>Exenatide 10 µg Twice Daily*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With metformin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intent-to-treat population, n</td>
<td>113</td>
<td>110</td>
<td>113</td>
</tr>
<tr>
<td>Mean change in A1c, %</td>
<td>+0.1</td>
<td>-0.4 (P≤.05)</td>
<td>-0.8 (P≤.0001)</td>
</tr>
<tr>
<td>Percentage of patients achieving A1c ≤7%</td>
<td>13</td>
<td>31.6 (P≤.05)</td>
<td>46.4 (P≤.05)</td>
</tr>
<tr>
<td>Mean change in weight, kg</td>
<td>-0.3</td>
<td>-1.6 (P≤.05)</td>
<td>-2.8 (P≤.0001)</td>
</tr>
<tr>
<td><strong>With sulfonylurea</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intent-to-treat population, n</td>
<td>123</td>
<td>125</td>
<td>129</td>
</tr>
<tr>
<td>Mean change in A1c, %</td>
<td>+0.1</td>
<td>-0.5 (P≤.05)</td>
<td>-0.9 (P≤.0001)</td>
</tr>
<tr>
<td>Percentage of patients achieving A1c ≤7%</td>
<td>8.8</td>
<td>32.6 (P≤.05)</td>
<td>41.3 (P≤.0001)</td>
</tr>
<tr>
<td>Mean change in weight, kg</td>
<td>-0.6</td>
<td>-0.9</td>
<td>-1.6 (P≤.05)</td>
</tr>
<tr>
<td><strong>With metformin + sulfonylurea</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intent-to-treat population, n</td>
<td>247</td>
<td>245</td>
<td>241</td>
</tr>
<tr>
<td>Mean change in A1c, %</td>
<td>+0.2</td>
<td>-0.6 (P≤.0001)</td>
<td>-0.8 (P≤.0001)</td>
</tr>
<tr>
<td>Percentage of patients achieving A1c ≤7%</td>
<td>9.2</td>
<td>27.4 (P≤.0001)</td>
<td>33.5 (P≤.0001)</td>
</tr>
<tr>
<td>Mean change in weight, kg</td>
<td>-0.9</td>
<td>-1.6 (P≤.05)</td>
<td>-1.6 (P≤.05)</td>
</tr>
</tbody>
</table>

*Exenatide 5 µg twice daily × 1 month, then 10 µg twice daily × 6 months. All P values are for treatment group compared with placebo.

Byetta® (exenatide) injection [prescribing information]. San Diego, Calif: Amylin Pharmaceuticals; 2006.

The safety and efficacy of exenatide was evaluated in three 30-week clinical trials involving 1446 patients with type 2 DM with inadequate glycemic control on metformin alone, sulfonylurea alone, or metformin in combination with sulfonylurea.

- Demographics: white, 991 (68.5%); Hispanic, 224 (15.5%); black, 174 (12.0%)
- Mean A1c values (baseline): 8.2% to 8.7%
- Design: 4-week placebo lead-in, then randomized to exenatide 5 µg twice daily, exenatide 10 µg twice daily, or placebo administered prior to morning and evening meals
- Existing oral antidiabetic agents continued
- All patients assigned to exenatide initiated treatment with 5 µg twice daily for 4 weeks, then either continued on 5 µg twice daily or increased dose to 10 µg twice daily
- Primary endpoint: mean change from baseline A1c at 30 weeks

**Results**

- Statistically significant, dose-dependent reduction in FBG and PPG through week 30
- Combined data: statistically significant reduction from baseline in mean FBG and PPG observed at week 30 compared with placebo
- Statistically significant greater proportion of patients achieved A1c ≤7% at week 30 than patients receiving placebo
- Decrease from baseline body weight at week 30 associated with exenatide 10 µg twice daily compared with placebo

**1-Year Clinical Results**

- In a cohort of 163 patients from the 30-week placebo-controlled trials who completed 52 weeks of treatment with exenatide 10 µg twice daily
  - A1c changes from baseline were −1.0% and −1.1% at 30 and 52 weeks of treatment, respectively
  - Accompanying changes from baseline in fasting plasma glucose were −14.0 mg/dL and −25.3 mg/dL
  - Body weight changes were −2.6 kg and −3.6 kg

Byetta® (exenatide) injection [prescribing information]. San Diego, Calif: Amylin Pharmaceuticals; 2006.
Liraglutide in Type 2 Diabetes: Results at 14 Weeks

• 165 patients with type 2 diabetes mellitus
• Treatment groups
  – Placebo
  – Liraglutide (0.65, 1.25, or 1.9 mg) daily
• Significant improvement in A1c with liraglutide versus placebo ($P<.0001$)
• Dose-related weight loss observed with liraglutide
• Gastrointestinal events were most common adverse drug reactions
  – Frequency decreased over time


14-week placebo-controlled study in 165 patients with type 2 DM with diet therapy alone (19%) or single oral agent
• Baseline A1c: 8.1% to 8.5%
• Randomized to 1 of 4 treatment groups: liraglutide 0.65, 1.25, or 1.9 mg daily or placebo
  – Patients taking oral therapy underwent 4-week washout period prior to start of trial
• Significant improvement in A1c in all liraglutide treatment groups
• Patients achieving A1c ≤7%
  – Liraglutide treatment (3 arms): 43% to 50%
  – Placebo: 8%
• Dose-related weight loss
  – 1.9 mg daily: -2.99 kg from baseline; -1.21 kg compared with placebo ($P=.039$)
• Generally well tolerated
  – Diarrhea: high-dose liraglutide 19.5%; placebo 12.5%
  – Nausea: high-dose liraglutide 10%
  – Frequency decreased over time

Amylin

- Endogenous peptide neuroendocrine hormone secreted by pancreas along with insulin in response to meals
- Secretion is delayed and diminished in type 2 DM and markedly diminished/absent in type 1 DM
- Actions
  - Suppresses endogenous glucagon production, particularly postprandial, resulting in decreased hepatic glucose production
  - Reduces PPG concentrations
  - Reduces gastrointestinal motility (centrally mediated)
  - Increased sense of satiety following meals (centrally mediated)

Pramlintide (Symlin®, Amylin Pharmaceuticals)

- Injectable agent
  - Analog of amylin with better physical properties than natural peptide
- When given in combination with insulin, pramlintide decreases PPG concentrations without increasing insulin levels
  - In patients with type 2 DM, 2-hour PPG was reduced by 3.4 mmol/L

### Pramlintide: Pooled Clinical Trial Results in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Pramlintide 120 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline A1c, %</td>
<td>9.3 (0.08)</td>
<td>9.1 (0.06)</td>
</tr>
<tr>
<td>Change in A1c at 6 months relative to baseline, %</td>
<td>–0.17 (0.07)</td>
<td>–0.57 (0.06)*</td>
</tr>
<tr>
<td>Placebo-subtracted A1c change at 6 months</td>
<td>–</td>
<td>–0.40 (0.09)*</td>
</tr>
<tr>
<td>Baseline weight, kg</td>
<td>91.3 (1.2)</td>
<td>92.5 (1.2)</td>
</tr>
<tr>
<td>Change in weight at 6 months relative to baseline, kg</td>
<td>+0.2 (0.2)</td>
<td>–1.5 (0.2)*</td>
</tr>
<tr>
<td>Placebo-subtracted weight change at 6 months, kg</td>
<td>–</td>
<td>–1.7 (0.3)*</td>
</tr>
<tr>
<td>Percentage change in insulin doses at 6 months: rapid/short-acting</td>
<td>+6.5 (2.7)</td>
<td>–3.0 (1.6)*</td>
</tr>
<tr>
<td>Percentage change in insulin doses at 6 months: long-acting</td>
<td>+5.2 (1.4)</td>
<td>–0.2 (1.3)*</td>
</tr>
</tbody>
</table>

*Statistically significant reduction compared with placebo (P<.05).

The table shows pooled results at 6 months from 2 long-term (26- to 52-week), randomized, double-blind, placebo-controlled studies of pramlintide in patients with type 2 DM using fixed-dose insulin.

- In both studies, pramlintide or placebo was added to the participants' existing DM therapies, including insulin ± sulfonylurea and/or metformin.

Demographic and baseline characteristics for the pramlintide-treated patients (n=871)
- Mean baseline A1c: 9.0% to 9.4%
- Mean age: 56.4–59.1 years
- Mean duration of DM: 11.5–14.4 years
- Mean BMI: 30.1–34.4 kg/m²

Results from a cohort of 145 patients who completed 2 years of pramlintide treatment
- Baseline-subtracted A1c: –0.40%
- Baseline-subtracted weight reduction: –0.36 kg

Most common adverse drug reactions
- Nausea (transient)
  - In clinical trials detailed here
  - Increased risk of hypoglycemia

Advantages: modest decrease in A1c and PPG; decrease in insulin need; smaller weight increases than with insulin monotherapy

Disadvantage: requires additional injection (pramlintide and insulin should not be mixed and must be administered separately using different syringes)

Symlin® (pramlintide acetate) injection [prescribing information]. San Diego, Calif: Amylin Pharmaceuticals; 2006.
J. M.—Question 4: True or False

The patient is reluctant to start insulin for several reasons. Which of the following concerns or opinions are valid?

A. Insulin therapy in type 2 diabetes mellitus is associated with marked hypoglycemia
B. Weight gain is inevitable with insulin therapy
C. Starting insulin will lead to more complications
D. Inhaled insulin (Exubera®) may be a good option because she hates the thought of needles
E. Using premixed insulin will improve blood glucose control

Please make your selection and click on the “Submit” button below.

Pop-Up Answers

A. False – Although hypoglycemia can occur, its frequency and severity is less in patients with type 2 diabetes compared to those with type 1 diabetes. In addition, the risk of hypoglycemia can be minimized with use of insulin analogues; careful timing of injections, meals and exercise; frequent SMBG; patient education about dosing adjustments and management of hypoglycemia.

B. False – Weight gain is often associated with insulin therapy. However, it can be modified with exercise and calorie restriction. In addition, metformin may mitigate some of the weight gain associated with insulin therapy. In general, the benefits of insulin therapy outweigh the risk of a slight increase in weight.

C. False – Insulin therapy is not associated with increased risk of macro- or microvascular complications associated with diabetes.

D. True – Inhaled insulin (Exubera) has an onset and duration of action similar to rapid-acting insulin analogs. However, both JM’s FPG and PPG are elevated. A better option to correct both pre- and postprandial glucose would be a twice daily premixed insulin analog. If only inhaled insulin were prescribed at this time, it is likely the patient will eventually require some longer-acting insulin coverage (and thus injections) in the near future to maintain adequate glycemic control.

E. True – A recent study compared once-daily basal insulin therapy (insulin glargine) with twice-daily premixed insulin lispro in insulin-naive patients. Twice-daily premixed insulin therapy was associated with a lower A1c value at study’s end and a greater change in A1c from pretherapy levels compared with daily insulin glargine ($P = 0.003$ and $P = 0.0068$, respectively). Premixed insulin therapy also resulted in improved postprandial blood glucose control.

(Jacober SJ, Scism-Bacon JL, Zagar AJ. A comparison of intensive mixture therapy with basal insulin therapy in insulin-naive patients with type 2 diabetes receiving oral antidiabetes agents. *Diabetes Obesity Metab.* 2006;8:448-455.)
Barriers to Insulin Use

- Patient limitations
  - Limited vision, dexterity, or mental capacity
- Patient fears
  - Injection
  - Hypoglycemia
  - Weight gain

Patients are often fearful about starting insulin therapy; it is important to provide adequate information and support.

Insulin therapy should not be used as a “threat” when discussing adherence with diet, exercise, and oral medication; due to the natural history of type 2 DM, even patients who comply with all therapeutic regimens generally need insulin at some point.

Education is key: eg, how to adjust doses, how to inject insulin, importance of SMBG.

Tailor therapy to fit the patient’s lifestyle: eg, take into account irregular hours, meals.

Provide follow-up early in therapy and maintain regular contact with patient until desired goal is met.

Regarding injection fears: injector devices are often more well received than syringes.

Regarding hypoglycemia: the risk of hypoglycemia is low in patients with type 2 DM; the patient should be educated about recognition of symptoms and ways to manage low blood glucose levels; frequent SMBG will provide helpful information if patient reports hypoglycemic episodes.

Regarding weight gain: explain that the benefit of glycemic control outweighs the minimal-to-moderate weight gain seen with insulin therapy; weight gain is less of a concern with insulin detemir; in addition, weight can be controlled with lifestyle modifications, such as diet and exercise.
Barriers to Insulin Therapy: Hypoglycemia in the UKPDS

The UKPDS is the largest long-term treatment study using insulin for type 2 DM.

- Hypoglycemic episodes were monitored as a measure of outcome during 10 years of treatment
- Nonobese and obese subjects randomized to begin with diet and exercise treatment had very little hypoglycemia, as was the case with subjects in the more obese subgroup treated with metformin; those assigned to sulfonylurea treatment had more hypoglycemia, but very few cases were severe; the groups treated with insulin from the start showed more hypoglycemia, as might be expected, with little difference between the nonobese and obese groups
- Most of the hypoglycemia was mild or moderate; severe hypoglycemic events occurred in 2% to 3% of subjects assigned to intensive glucose control each year
- This rate is certainly not trivial, but it is far less than the rate seen with intensive treatment of type 1 DM patients in the Diabetes Control and Complications Trial

• 26 Patients with type 2 DM
  – FBG >8 mmol/L
  – Previously treated with maximum doses of glyburide (>10 mg/d) or glipizide (>15 mg/d)
  – Baseline A1c (average): 10%
  – Randomized to neutral protamine Hagedorn (NPH) insulin twice daily alone (13 patients) or insulin at bedtime plus metformin 2 g daily (13 patients)

• Measured parameters: body weight, basal metabolic rate (BMR), energy intake, glucosuria

• Results
  – Similar improvement in glycemic control in both groups
  – Increased body weight
    – Insulin alone: 7.5 ± 1.6 kg
    – Insulin + metformin: 3.8 ± 0.8 kg (P<.05 compared with insulin alone)
  – Improved glycemic control associated with decreased BMR and decreased glucosuria
    – BMR and glucosuria changes similar in both groups, but metformin also decreased energy intake

Insulin Therapy and Weight Gain

- Patients who gain the most weight after insulin initiation are those who
  - Had the worst metabolic control before the intensification of treatment
  - Had greater weight loss prior to insulin initiation
- Contrary to common beliefs, no evidence exists
  - That weight gain after insulin initiation is associated with deterioration of the lipid profile, arterial hypertension, or an excess risk for cardiovascular events
- All studies conducted to date with insulin detemir have shown significantly less weight gain compared with NPH insulin over the 4 to 12 month study periods

- Insulin therapy induces weight gain in patients with type 2 diabetes. An intriguing fact is that most of the excess weight gain occurs within the first 2 years following initiation of insulin treatment. This suggests that most of the weight gain is a “catch-up” re-gain, allowing patients to return to the weight they would have in the absence of diabetes-induced weight loss.1
- Patients who gain the most weight after insulin initiation are those who had the worst metabolic control before the intensification of treatment and those who had greater weight loss prior to insulin initiation.1
- Contrary to common beliefs, no evidence exists that weight gain after insulin initiation is associated with deterioration of the lipid profile, arterial hypertension, or an excess risk for cardiovascular events.1
- All studies conducted to date with the insulin analog detemir in patients with type 2 diabetes have shown significantly less weight gain compared with NPH insulin over the 4 to 12 month study periods.2,3

1. Larger E. Weight gain and insulin treatment. Diabetes Metab. 2005;31:4S51-4S56.
### Inhaled Insulin in Combination With Oral Antidiabetic Therapy

#### Results of Two 24-week, Active-control, Open-label Trials in Patients With Type 2 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Study E</th>
<th>Study F</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inhaled Insulin + Met</td>
<td>Inhaled Insulin + Met</td>
</tr>
<tr>
<td></td>
<td>SU</td>
<td>SU + Glyburide</td>
</tr>
<tr>
<td><strong>Patients, n</strong></td>
<td>113</td>
<td>103</td>
</tr>
<tr>
<td><strong>A1c, %</strong></td>
<td>10.5</td>
<td>10.6</td>
</tr>
<tr>
<td>Baseline A1c</td>
<td>9.6% to 12%</td>
<td>8% to 9.5%</td>
</tr>
<tr>
<td>Baseline A1c</td>
<td>10.6</td>
<td>10.6</td>
</tr>
<tr>
<td>Mean Δ from baseline</td>
<td>-2.2</td>
<td>-1.8</td>
</tr>
<tr>
<td>FPG, mg/dL</td>
<td>241</td>
<td>237</td>
</tr>
<tr>
<td>Baseline</td>
<td>241</td>
<td>237</td>
</tr>
<tr>
<td>Mean Δ from baseline</td>
<td>-46</td>
<td>-47</td>
</tr>
<tr>
<td>A1c &lt;7%, %</td>
<td>20.4</td>
<td>14.6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80.8</td>
<td>79.5</td>
</tr>
<tr>
<td>Baseline</td>
<td>80.8</td>
<td>79.5</td>
</tr>
<tr>
<td>Mean Δ from baseline</td>
<td>3.6</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**SU** = sulfonylurea; **Met** = metformin.

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**Powder Formulation (Exubera®, Pfizer)**

- Approved in United States February 2006
- Rapid-acting, dry powder inhaled via product-specific device
  - Onset of activity: approximately 10 minutes after inhalation
- Indicated as prandial insulin therapy in patients with types 1 and 2 DM
  - Type 1: in combination with long-acting insulin
  - Type 2: alone or in combination with oral antidiabetic agents or long-acting insulin
- Clinical trial data
  - Study E: inhaled insulin + sulfonylurea was superior to metformin + sulfonylurea in reducing A1c in patients with high baseline A1c (9.6% to 12%), and comparable to metformin + sulfonylurea in patients with lower baseline A1c; comparable reductions in FPG and in percentage of patients reaching A1c target
  - Study F: inhaled insulin + metformin was superior to metformin + glyburide in reducing A1c in patients with high baseline A1c (9.6% to 12%), and comparable to metformin + sulfonylurea in patients with lower baseline A1c; comparable reductions in FPG and in percentage of patients reaching A1c target
  - Rate of hypoglycemia was slightly greater in those receiving inhaled insulin
- Not recommended for patients with underlying lung disease (eg, chronic obstructive pulmonary disease, asthma)
- Cigarette smoking increases insulin exposure 2- to 5-fold; Exubera is contraindicated in patients who smoke or if the patient quit smoking less than 6 months prior to proposed initiation of therapy

**Liquid Formulation (AERx®iDMS; Novo Nordisk)**

- Currently in phase 3 clinical trials
- Data to date suggest that this formulation is comparable to subcutaneous insulin in reducing A1c but may be associated with lower FPG and reduced risk of hypoglycemic episodes

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J. M.—6 Weeks After Starting Insulin

- Prescribed insulin regimen
  - 12 U 70/30 premixed insulin aspart (NovoLog® Mix) before dinner
  - Increase every 3 days by 2 U for 2-hour PPG >140 mg/dL

- 6 weeks later
  - Dose: 28 U before dinner
  - 4-lb weight gain

<table>
<thead>
<tr>
<th></th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
<th>Bedtime</th>
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- J. M. finally agrees to start insulin therapy after much discussion with her physician
- The initial prescribed dose is 12 U 70/30 premixed insulin aspart (NovoLog® Mix 70/30) before dinner
- She is instructed to increase the dose by 2 U every 3 days if her 2-hour postdinner glucose is >140 mg/dL; she is also advised to call with any problems or concerns
- She returns 6 weeks later: her current dosage is 28 U 70/30 premix insulin aspart at dinnertime; she reports that she is feeling better, and her weight has increased by 4 lb
- Her blood glucose log reveals: FPG is markedly reduced, with high PPG after breakfast and lunch being the driving force behind the preprandial lunch and dinner glucose levels
Breakfast Lunch Dinner

Plasma Insulin (µU/mL)

Basal insulin = 40% to 50% of total daily insulin

Bolus or mealtime insulin = 50% to 60% of total daily insulin

Ideal Insulin Replacement Pattern
Long-acting Insulin Glargine or Detemir at Bedtime Only

Breakfast  Lunch  Dinner

Glargine Detemir

Plasma Insulin (µU/mL)

0400 0800 1200 1600 2000 2400 0400

Time of Day
Another option in selected patients may be to use a premixed insulin 3 times per day; however, this approach will not have the flexibility of titrating the rapid acting insulin separately.
Rationale for Premixed Insulin Analogs

- Insulin analogs more closely mimic insulin secretion\(^1\)
  - Low rate of hypoglycemia; no NPH insulin
- Convenient dosing\(^1,2\)
  - Once daily with option to intensify
  - Mealtime administration
- Coverage of FPG and PPG\(^1\)
  - Better A1c control and PPG control than with basal insulin analogs alone
- 3 products available: aspart 70/30 and lispro 75/25 or lispro 50/50\(^1\)
- 1-, 2-, or 3-injection regimens\(^2\)

NPH = neutral protamine Hagedorn.


Rationale for Premixed Insulin Analogs

- Insulin analogs were developed to more closely mimic physiologic secretion
- Analogs have a more predictable onset and duration of action compared with human insulin formulations
- Premixed insulin analog formulations provide coverage for both basal (FPG) and prandial (PPG) insulin needs
  - In addition, the rapid absorption of premixed insulin analogs allows for greater PPG control than regular insulin in premixed human insulin formulations
- Because of the rapid action of the prandial component, premixed insulin analogs also can be administered closer to mealtimes
- Currently, 3 premixed insulin analog products are available in the United States: insulin aspart 70/30, insulin lispro 75/25, and insulin lispro 50/50


• Open-label, randomized, single-dose, 3-way crossover trial
  – 61 patients
  – Insulin aspart and lispro premix injected immediately prior to test meal
  – Human insulin injected 15 minutes prior to test meal
• Postprandial glycemic control (5-hour PPG)
  – Analog mixes provided better control than human mixes
  – Insulin aspart 70/30 superior to insulin lispro 75/25 or human insulin mixes (\(P=.05\) and \(P=.001\), respectively)

J. M.—Question 5

What is the next step in treatment for this patient?

A. Add 12 U 70/30 premixed insulin aspart with breakfast and monitor blood glucose closely
B. Add 12 U 70/30 premixed insulin aspart with breakfast and stop glimepiride
C. Add 12 U 70/30 premixed insulin aspart with breakfast and stop all oral antidiabetic agents
D. Add repaglinide with breakfast and stop glimepiride
E. Start basal-bolus insulin therapy and discontinue predinner 70/30 premixed insulin aspart

Please make your selection and click on the “Submit” button below.

Pop-Up Answers

A. Best option: JM’s high PPG is the driving force behind elevated glucose levels seen before lunch and dinner. 70/30 premixed will provide postbreakfast glycemic control that will last just beyond the dinner hour.

B. Possible, but not best option: Prebreakfast 70/30 should provide glycemic control throughout the day, and it is likely that β-cell failure is complete (thus rendering little effect from the SU). However, it would be best to make a single change in the patient’s regimen at this time, while monitoring her blood glucose levels (via SMBG) closely.

C. Possible, but not best option: This will address the issue of postbreakfast hyperglycemia, provide basal coverage for the entire day. It is likely that β-cell failure is nearly complete, but metformin may still be useful in combination with insulin in this patient.

D. Possible, but not the best option: Of the two meglitinides, repaglinide is associated most with control of overnight and pre-prandial glucose concentrations. Since this issue has been well covered with the predinner 70/30 premixed insulin aspart. In addition, switching from a SU to a shorter acting secretagogue will not be as effective in a patient who requires insulin for glucose control.

E. Possible, but not the best option: This patient was hesitant to use insulin initially. This change in strategy would involve 3 additional injections of insulin each day. Patient acceptance and adherence to such a regimen is unlikely.
J. M.—Treatment Outcome

- Started on 12 U insulin aspart 70/30 premixed before breakfast
  - Subsequently increased to 24 U
  - Postbreakfast blood glucose: 130–140 mg/dL
- Predinner insulin dose decreased from 28 U to 24 U
- Glimepiride discontinued

- Prebreakfast insulin was prescribed for J. M., which provided excellent postprandial (and daytime) glycemic control
- To compensate for the reduction in predinner glucose levels, the dose of predinner 70/30 insulin was decreased
- In light of the fact that β-cell failure was near-complete, glimepiride was eventually discontinued
Twice-daily Insulin Aspart 70/30 Premix Versus Once-daily Insulin Glargine

- Compared safety and efficacy of twice-daily aspart 70/30 premix to once-daily glargine in 233 insulin-naive patients
  - Baseline A1c ≥8%
  - Receiving metformin ≥1000 mg daily ± other oral agents for ≥3 months
- Study regimen
  - Metformin optimized to 1500–2550 mg daily
  - 70/30 premix: started at 5–6 U twice daily, then titrated to target blood glucose
    - Morning dose adjusted based on predinner glucose level; evening dose adjusted based on FPG
  - Glargine: started at 10 U at bedtime, then titrated to target blood glucose
    - Adjusted based on FPG
- At 28 weeks
  - Mean A1c value lower in 70/30 premix group compared with glargine group
    - Mean decrease in A1c was −2.79% with 70/30 and −2.36% with glargine
    - Significantly greater percentage of patients achieved A1c goals with 70/30 premix
  - Both groups experienced weight gain during treatment
    - 70/30 premix: 5.4 ± 4.8 kg
    - Glargine: 3.5 ± 4.5 kg

“Real-world” Experience: Presented at June 2006 ADA Meeting

- Retrospective cohort study looked at ~8200 patients receiving either once-daily basal analog insulin, twice-daily premixed analog insulin, or twice-daily 70/30 premix human insulin
- Twice-daily premixed analog insulin was more effective in reducing A1c than once-daily basal analog insulin

Case Study Summary: J. M.

- 55-year-old Latina woman
- Increased urination, thirst, and fatigue and a 4-lb weight loss
- Infrequent self-monitoring of blood glucose (SMBG)
  - Fasting blood glucose (FBG): 160–200 mg/dL
  - Preprandial: 150–170 mg/dL
- Current treatment (Rx)
  - Glimepiride 2 mg daily
  - Metformin 1000 mg twice daily
- Other medical problems
  - Hypertension (Rx—lisinopril)
  - Dyslipidemia (Rx—fenofibrate, atorvastatin)
Case Study: P. C.

68-year-old Chinese man with type 2 diabetes mellitus for 6 years

- Lifestyle
  - 2 bowls of rice as part of his daily meal intake
  - Walks daily
- Current therapy
  - Glyburide 5 mg twice daily
  - Metformin 850 mg twice daily
  - NPH insulin 24 U at bedtime
- SMBG 2 times daily
  - Notes FBG occasionally >200 mg/dL
- Other medical problems
  - Hypertension (Rx—lisinopril 10 mg, hydrochlorothiazide 12.5 mg)
  - Dyslipidemia (Rx—gemfibrozil 600 mg twice daily)

Case Study: P. C.

- 68-year-old Chinese man who received a diagnosis of type 2 DM 6 years ago comes in for a routine follow-up examination
- He states that until 8 weeks ago, he was doing quite well but now is noting more frequent FBG >200 mg/dL; he does SMBG twice daily
- His current DM therapy consists of glyburide 5 mg at bedtime and metformin 850 mg twice daily; he initially did well with oral agents, but insulin therapy became necessary approximately 3 years ago; he is currently using 24 U NPH insulin at bedtime
- He tries to be consistent about watching his carbohydrate intake, particularly after seeing a dietician 2 years ago; he is a retired businessman who lives with his wife of 40 years; he does not smoke or drink alcoholic beverages and keeps fit by walking for 45 minutes every day around 3:00 to 4:00 PM
- In addition to DM, the patient has hypertension (treated with lisinopril and hydrochlorothiazide) and dyslipidemia (treated with gemfibrozil)
P. C.—Patient Examination

- **Physical examination**
  - Height: 64 in
  - Weight: 124 lb
  - BMI: 21.3 kg/m²
  - BP: 126/72 mm Hg
  - No evidence of neuropathy, retinopathy, or peripheral vascular disease

- **Laboratory values**
  - A1c: 8.2%
  - GADA-positive
  - Lipids
    - Total cholesterol: 186 mg/dL
    - HDL-C: 45 mg/dL
    - LDL-C: 96 mg/dL
    - TG: 220 mg/dL
  - Urine
    - Albumin-to-creatinine ratio: 26 µg/mg
      (normal <30 µg/mg)

GADA = glutamic acid decarboxylase antibody; LDL-C = low-density lipoprotein cholesterol.

What do the physical examination and laboratory results tell us about P. C.?

- P. C. is not overweight (BMI is calculated to be 21.3 kg/m²; normal weight status: 18.4–24.9 kg/m²)
- He has no evidence of peripheral neuropathy, retinopathy, peripheral vascular disease, or nephropathy (albumin-to-creatinine ratio <30 µg/mg)
- A1c of 8.2% is 1.2% above goal for glycemic control
- Presence of glutamic acid decarboxylase antibodies (GADAs) indicate an autoimmune process directed against islet cells
- Hypertension is under control
- Dyslipidemia is not well controlled
- Low-density lipoprotein cholesterol (LDL-C) is only slightly below recommended target (<100 mg/dL)
- HDL-C is only slightly greater than recommended target (>40 mg/dL)
- Triglycerides are markedly greater than recommended target (<150 mg/dL)
P. C.—Question 1

Is it possible that this patient has latent autoimmune diabetes in adults (LADA)?

A. Yes
B. No

Please make your selection and click on the "Submit" button below.

Pop-Up Answers

A. Correct - Approximately 10% of individuals diagnosed with type 2 diabetes actually have LADA. This gentleman has many characteristics seen in patients with LADA, including normal weight status (although not diagnostic for LADA since many patients are overweight), and initial insulin independence but with need for insulin therapy within a relatively short time after diagnosis. In addition, serum antibody analysis revealed the presence of one of 4 known islet autoantibodies against islet cells (ICAs), glutamic acid decarboxylase (GADAs), tyrosine phosphatase (IA-2 antibodies), and insulin (IAA).

B. Incorrect – The presence of GADAs indicated an ongoing autoimmune component to PC’s diabetes
4 Major Categories of DM

- Type 1
  - Immune-mediated DM (also referred to as type 1a)
  - Idiopathic DM (also referred to as type 1b)
- Type 2
  - Characterized by insulin resistance, impaired insulin secretion, and abnormal splanchnic glucose uptake
- LADA
- Gestational
- Other
  - Etiologies include surgery, drugs, malnutrition, infection, other illnesses
  - Some classify LADA within this group

LADA

- Phenotypic type 2 patient
- Positive for islet autoantibodies
  - GADA
- Initially insulin independent
- May account for 10% of diagnosed type 2 diabetes


LADA

- Phenotypic type 2 patients who are positive for autoantibodies against
  - Islet cells
  - GAD
  - Insulin: much less common than in patients with type 1 DM
  - Tyrosine phosphatase: much less common than in patients with type 1 DM
- Etiology of DM in approximately 10% of individuals diagnosed with type 2 DM
- Differences in antibody types, T-cell stimuli, and genetics suggest unique underlying processes behind type 1 DM and LADA

Diagnostic Criteria

- Adult age at onset
- Presence of islet autoantibodies, particularly GADAs
- Initial lack of requirement for insulin therapy (at least 6 months) after diagnosis

P. C.—2 Weeks After Initial Visit

Current Rx: glyburide 5 mg twice daily; metformin 850 mg twice daily; NPH 24 U at bedtime

Blood Glucose Log Showing FBG and PPG, mg/dL

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- The patient should monitor 2-hour PPG at least once daily, in addition to morning FBG and premeal blood glucose
- He returns 4 weeks later with blood glucose logs; the results for the past week are shown; he states that these are consistent with the results for the past month
- Blood glucose logs reveal
  - Elevated FBG most days
  - Elevated PPG after every meal
- When questioned about his diet, P. C. reveals that he eats 2 bowls of white rice with dinner, which has been a life-long dietary habit
Factors Contributing to Inadequate Glycemic Control

- Failure of clinicians to adopt a “treat-to-target” approach
- Suboptimal use of available therapies
  - Delayed use of combination therapy
  - Delayed use of insulin
- Suboptimal patient adherence to lifestyle measures or pharmacologic therapy
- Lack of optimal systems for healthcare delivery

As mentioned, the majority of patients do not achieve recommended goals
Factors are physician and patient related
Target goals can be achieved with early initiation of combination therapy and persistent titration of doses (ie, treat to target)
  - Population-based study among members of a health maintenance organization in the northwestern United States (1994–2002) revealed that A1c averaged 9.6% before combination therapy was initiated
Progression to insulin use also delayed: current NHANES data suggest marked underuse of insulin therapy
  - May be due to perceived complexity of use, belief that insulin is not effective, or fear of hypoglycemia or weight gain
Patients often fail to fully adhere to prescribed treatment
  - In a CADRE survey of 125 doctors, patient nonadherence and lack of motivation were cited as significant obstacles to achieving goals
Healthcare systems not structured for chronic conditions or fragmentation of services also contribute to ineffective DM management

P. C.—Question 2

Based on the patient’s SMBG log, what is the next logical step in treatment?

A. Increase NPH to 28 U
B. Discontinue NPH and use 70/30 before dinner
C. Discontinue NPH and use insulin glargine or detemir
D. Discontinue NPH and use exenatide predinner
E. Check 3:00 AM blood glucose

Please make your selection and click on the "Submit" button below.

Pop-Up Answers

A. This may be acceptable; however, PC’s blood glucose log shows fasting levels of 115 mg/dL and 123 mg/dL, which may place him at an increased risk for hypoglycemia.

B. This is a reasonable option as it will control PC’s elevated postprandial glucose levels.

C. This is not recommended. PC has postdinner hyperglycemia and fasting blood glucose values are generally within a reasonable range.

D. This is not recommended. Exenatide induces insulin release via a unique mechanism of action, and has been shown to reduce both fasting and postprandial glucose levels. However, exenatide is not a replacement for insulin.

E. Correct! A review of PC’s blood glucose log indicates that he has two fasting blood glucose levels >200 mg/dL. Nocturnal hypoglycemia with rebound needs to be excluded.
As suspected, SMBG showed a considerable drop in blood glucose in the early hours of the morning, followed by high FBG the following day.

When blood glucose falls rapidly during the night, the liver is triggered to release glucose into the bloodstream, resulting in hyperglycemia at awakening.

Based on this blood glucose log, P. C.’s bedtime NPH insulin dose was reduced to 20 U at bedtime, and an evening snack was added to his meal plan.
As you can see, P. C.’s blood glucose pattern is consistent with the activity profile of NPH insulin.

Based on his blood glucose logs, the prescribed therapy was:
  - Reduce bedtime NPH dose
  - Add bedtime snack
P. C.—3 Months Later

Current Rx: glyburide 5 mg twice daily; metformin 850 mg twice daily; NPH 20 U at bedtime

Blood Glucose Log Showing FBG and PPG, mg/dL

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- P. C. does well for about 3 months, then notices that his FBG is increasing again, and he is more fatigued and losing weight; although he had reduced the frequency of SMBG, he is asked to increase testing again and come in with a new blood glucose log after 1 week (above)
- As you can see, P. C. is experiencing marked postprandial hyperglycemia after dinner; in addition, his A1c reveals evidence that loss of glycemic control may be occurring on the current regimen, most likely due to disease progression
P. C.—Question 3

What changes in this patient’s diabetes treatment regimen would you recommend at this time?

A. Discontinue NPH and start insulin detemir at bedtime
B. Discontinue NPH and start inhaled insulin
C. Discontinue NPH and start 70/30 premixed insulin aspart before dinner
D. Discontinue NPH and use 70/30 premixed insulin aspart twice daily
E. Start patient on self-mix of rapid insulin and NPH before dinner and discontinue bedtime NPH

Please make your selection and click on the “Submit” button below.

A. **Appropriate intervention:** Taking into consideration P.C.’s daily afternoon walk, this is an appropriate intervention to reduce the risk of hypoglycemia. Clinical trials data have shown that, compared with NPH in combination with oral antidiabetic treatment, insulin detemir is associated with
   - Significantly less within-patient variation of prebreakfast and predinner plasma glucose
   - Lower risk of hypoglycemia and less weight gain; lower risk of nocturnal hypoglycemia
   - Significantly greater proportion of patients achieving A1c <7% in absence of hypoglycemia
   - This option will control PC’s fasting glucose; however, PC is experiencing marked postprandial hyperglycemia after dinner, which needs to be addressed.

B. **Reasonable new option (under certain conditions):** This would be reasonable if we were only trying to control PC’s postprandial hyperglycemia; however, because we are looking to control more symptoms (e.g., fasting blood glucose, elevated postbreakfast glucose), this would not be a viable option.

C. **Reasonable option:** This is a reasonable intervention because it will control PC’s postprandial hyperglycemia and fasting blood glucose; however, because of P.C.’s daily afternoon walk, he may be at increased risk for hypoglycemia.

D. **Reasonable option:** This is a reasonable option if P.C. will benefit from twice-daily dosing. Because of elevated postbreakfast glucose; however, predinner premix will lower fasting glucose and improve postbreakfast glucose.

E. **Possible option:** There are challenges associated with mixing insulins, and this regimen may be more complicated.
Insulin Replacement Strategies

- Prandial (bolus)
  - Mimics response of endogenous insulin to meals
- Basal
  - Mimics constant release of endogenous insulin, regulating lipolysis and hepatic glucose output
- Correction-dose supplementation
  - Regulate pre- or between-meal hyperglycemia


Review of Insulin Replacement Strategies in Patients With Type 2 DM

- Prandial
  - Designed to mimic response of endogenous insulin to meals
  - Use of short-acting insulin 10–15 minutes prior to each meal
- Basal
  - Designed to mimic low-level constant release of endogenous insulin
  - Use of long-acting insulin once or twice daily
- Correction-dose supplementation (of regular insulin or rapid-acting analog)
  - Given every 4 or 2 hours, respectively
  - Correction-dose therapy differs from sliding scale monotherapy in that correction doses are proportionate to daily requirement and are offered as a supplement to, not a replacement for, scheduled therapy
    - “Sliding” scale insulin to correct hyperglycemia—no longer recommended by most practitioners because this practice is associated with erratic glycemic control and increased risk of hypoglycemic episodes

Pharmacokinetic Profiles of Human Insulins and Analogs

- Inhaled insulin*: 6 hours
- Aspart, lispro, glulisine (4–6 hours)
- Regular (6–10 hours)
- NPH (12–20 hours)
- GLargine, detemir (20–26 hours)

*insulin human [rDNA] origin inhalation powder
Activity of Insulin Analogs

- **Rapid-acting (lispro, aspart, glulisine)\(^1,2\)**
  - Onset: 5–20 minutes
  - Peak: 30 min–3 hours
  - Effective duration: 3–6 hours

- **Long-acting (glargine, detemir)\(^1,2\)**
  - Onset: 50 min–4 hours
  - Effective duration: up to 24 hours
  - Similarity of these 2 analogs shown in recent head-to-head pharmacokinetics/pharmacodynamics study\(^3\)

2. Data obtained from individual product prescribing information.

From a clinical standpoint, the pharmacodynamic profile of insulin analogs is more important than the pharmacokinetic properties with regard to effects on blood glucose concentrations.

**Rapid-acting Analogs**
- Used as bolus therapy to control PPG excursions or as continuous subcutaneous therapy via insulin pump
  - Lispro (Humalog\(^\circ\), Eli Lilly)
  - Aspart (NovoLog, Novo Nordisk)
  - Glulisine (Apidra\(^\circ\), Sanofi-Aventis)

**Long-acting Analogs**
- Used for basal insulin therapy alone (basal therapy) or with rapid-acting insulin (basal-bolus therapy) and/or oral antidiabetic agents
  - Glargine (Lantus\(^\circ\), Sanofi-Aventis)
  - Detemir (Levemir\(^\circ\), Novo Nordisk)
P. C.—6 Weeks Later

Current Rx: insulin detemir 28 U at bedtime; glyburide 5 mg twice daily; metformin 850 mg twice daily

Blood Glucose Log Showing FBG and PPG, mg/dL

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- P.C. was started on insulin detemir 20 U at bedtime; he increased the dose by 2 U every 3 days for FBG >100 mg/dL
- Oral medications (glyburide and metformin) remained the same
- 6 weeks later, P.C. returns with the glucose log shown; he is using 28 U insulin detemir at bedtime
- Although FBG improved and he has experienced no nocturnal hypoglycemia, P. C. still has significant postdinner hyperglycemia; when questioned about his evening meal, he states that he still has 2 bowls of white rice with dinner—he does not feel that he can change this habit because he has done this all his life
P. C.—Question 4

How could this patient’s postdinner hyperglycemia be managed?

A. Have dietician emphasize need for patient to eat only 1 bowl of rice with dinner
B. Suggest changing to brown rice with dinner
C. Change dinnertime glyburide to repaglinide
D. Discontinue glyburide and start rapid-acting insulin predinner (injected or inhaled)
E. Discontinue predinner glyburide, start rapid-acting insulin predinner, and reduce bedtime insulin detemir dose

Please make your selection and click on the “Submit” button below.

Pop-Up Answers

A. Reasonable option, but not the BEST: While the patient could use ongoing nutritional education, it is unlikely that he will adhere to the dietary recommendation.

B. Reasonable option, but not the BEST: The patient will likely need more than simply this dietary change to effect glycemic control. However, brown rice is a better choice than white rice. In a study by Miller JB et. al., the glycemic index (GI; the relative rate at which glucose appears in the blood after the ingestion of carbohydrate; compared with that of white bread [GI = 100]) and the insulin response of various foods were tested and compared:

The GI of white and brown rice were similar
The insulin response for brown rice was significantly lower than for white rice

C. Poor option: The concomitant use of repaglinide and gemfibrozil is contraindicated. Such use may markedly enhance and prolong the blood glucose-lowering effects of repaglinide, placing the patient at risk of severe and prolonged hypoglycemia. Furthermore, the patient is already on basal insulin and a long-acting SU, so effectiveness will be limited.

D. Reasonable option, but not the BEST: This choice may be effective for dinner but PC will still need coverage for breakfast, which would be lacking due to the discontinuation of glyburide.

E. Most appropriate option: This option allows greater flexibility in dose adjustment. A significant amount of experience exists using rapid-acting insulin before meals with dose adjustments clearly understood.
Blood Glucose Log Showing FBG and PPG, mg/dL

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- P. C.’s physician discontinued his evening glyburide and added premeal insulin aspart at dinner time; P. C. also agreed to use brown rice instead of white rice; his predinner insulin dose is started at 4 U (1 U/15 g carbohydrate), and P. C. is told to test his 2-hour postdinner glucose regularly
- In addition, the insulin detemir dose was decreased to 24 U to avoid early-morning hypoglycemia
- A repeated A1c measurement 3 months later was 7.2%
P. C.—9 Months Later

- Patient reports weight loss, fatigue, and tingling in feet
- Current therapy
  - Metformin 850 mg twice daily
  - Glyburide 5 mg each morning
  - Insulin detemir 30 U at bedtime
  - Insulin aspart 6–10 U before dinner
- Laboratory results
  - A1c: 8.7%
  - Total cholesterol: 245 mg/dL
  - LDL-C: 100 mg/dL
  - Urine albumin-to-creatinine ratio: 145 μg/mg (normal <30 μg/mg)

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- P. C. does well on this regimen for 9 months; at this point, his A1c starts to increase, and he reports some tingling in his feet, weight loss, and fatigue; P. C. reports increasing shortness of breath and difficulty completing his afternoon walk, having to stop frequently to rest
- P. C.’s most recent laboratory results show an increase in A1c and microalbuminuria and hyperlipidemia
- P. C.’s insulin therapy consists of 6–10 U insulin aspart prior to dinner, and 30 U insulin detemir at bedtime
- P. C.’s glucose log (shown) reveals postprandial hyperglycemia after breakfast and lunch and increased predinner blood glucose
P. C.—Question 5

Based on P. C.’s symptoms and laboratory values, what changes should be made in his therapy?

A. Discontinue ACE inhibitor and start ARB
B. Add ARB to ACE inhibitor
C. Schedule electrocardiogram
D. Schedule exercise tolerance test with imaging
E. Refer to cardiology department

Please make your selection and click on the “Submit” button below.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

A. Not recommended: PC is not complaining of cough or adverse events related to ACE inhibitor treatment, so this is not recommended.

B. Good option: PC’s microalbumin has increased with improved glucose control, therefore adding and ARB to his current ACE inhibitor treatment may be complimentary in decreasing his microalbumin.

C. Not the best option: An ECG is not a reliable diagnostic tool for determining coronary artery disease status in patients with diabetes mellitus.

D. Good option: Exercise tolerance testing is an important and diagnostic tool for assessing patients with suspected or known ischemic heart disease.

E. Most appropriate option: Given PC’s elevated microalbumin, dyslipidemia, and increase in shortness of breath, PC most likely has significant coronary artery disease, so a referral to see a cardiologist is appropriate at this time.
Complications of Diabetes

- **Cardiovascular disease**
  - Death rates are 2–4 times higher in adults with diabetes compared with those without diabetes
  - 73% of patients have BP $\geq 130/80$ mm Hg or use prescription medications for hypertension

- **Stroke**
  - 2–4 times greater risk

- **Blindness**
  - 12,000–24,000 new cases of blindness per year

- **End-stage renal disease**
  - Leading cause of kidney failure in United States

- **Peripheral neuropathy**
  - 60% to 70% have mild-to-severe nervous system damage

- **Nontraumatic lower-limb amputations**
  - $>60\%$ occur in patients with diabetes


- The consequences of poor glycemic control include serious DM-related complications
  - Diabetes was sixth leading cause of death in United States in 2002 (as listed on death certificates)
    - Likely to be underreported as a cause of death
    - Overall risk for death among people with DM is about 2 times that among people of a similar age without DM

- **Microvascular complications include retinopathy, nephropathy, and neuropathy**
  - Diabetes is leading cause of new cases of blindness, with diabetic retinopathy causing 12,000–24,000 new cases per year
  - Diabetes is leading cause of kidney failure
  - Majority of patients have some form of neuropathy, which is associated with impaired sensation in extremities and slowed digestion

- **Macrovascular complications include myocardial infarction, stroke, and peripheral vascular disease**
  - Heart disease and stroke account for $\sim65\%$ of deaths in patients with DM
  - Majority of nontraumatic lower-limb amputations occur in patients with DM
    - 82,000 performed in 2002

- In patients with LADA, the frequency of microvascular and macrovascular complications is similar to that in patients with type 2 DM
- One study showed that even after excluding patients with known diabetes or A1c $\geq 7\%$ and those with history of cardiovascular disease, each 1% increase in A1c was associated with a 26% increase in risk of death (independent of age, blood pressure, serum cholesterol, BMI, and smoking habits)$^4$

Other Health-related Goals for Diabetes Management

- **BP**
  - Systolic <130 mm Hg; diastolic <80 mm Hg

- **Lipids**
  - LDL-C <100 mg/dL
  - HDL-C >40 mg/dL (men); >50 mg/dL (women)
  - TG <150 mg/dL

- **Cardioprotection**
  - Recommended antiplatelet therapy for
    - Primary prevention (aspirin 75–162 mg/d): Type 1 and 2: >40 years or with additional risk factors
    - Secondary prevention (aspirin: 75–162 mg/d) for those with diabetes and history of CVD
  - Warning: not recommended for patients <21 years of age (people <30 years have not been studied)

- **Smoking cessation**

Based on P. C.’s blood glucose log, what changes should be made in his therapy at this time?

A. Add prebreakfast insulin aspart
B. Add prebreakfast and prelunch insulin aspart and stop sulfonylurea
C. Discontinue insulin detemir, predinner insulin aspart, and sulfonylurea; start 70/30 premix twice daily
D. Discontinue sulfonylurea; add morning dose of insulin detemir and prebreakfast and prelunch insulin aspart

**Pop-Up Answers**

A. **Good option, but not the BEST:** This option will cover breakfast, but PC needs postlunch coverage

B. **BEST choice:** This regimen will provide breakfast and lunch coverage.

C. **Good option, but not the BEST:** This is a reasonable option, but does not have the flexibility of a basal bolus regimen.

D. **Good option, but not the BEST:** There is currently no indication that PC requires a split dose of insulin detemir.
Basal-bolus Insulin Therapy

- Basal insulin suppresses glucose production between meals and overnight
  - Nearly constant insulin levels
- Bolus (prandial) insulin limits hyperglycemia after meals
  - Immediate increase and sharp peak at 1 hour

The ideal insulin replacement pattern would mimic physiologic insulin release (ie, low constant levels of insulin throughout the day with higher levels induced by meals)

Guidelines for Basal-bolus Insulin Therapy

• Starting insulin dose = 0.2–0.5 U/kg daily
  – 50% to 60% as basal insulin
  – 40% to 50% as bolus
• Basal insulin adjustments
  – Adjust up or down based on FPG of past 2 days
  – Do not increase >1 time per week


Steps in Initiating Basal-bolus Therapy
• Establish dosing regimen based on the patient’s insulin needs, determined by glucose and A1c levels, as well as exercise and eating habits
• Adjust doses based on the results of SBGM
  – SBGM should include FBG and PPG, particularly at initiation of therapy and if therapy is changed
  – Frequent SBGM helps patients identify and respond rapidly to problems with glycemic control
• A generally used starting dose for insulin therapy is 0.2 U/kg daily
  – Option: insulin U daily is equal to FPG in mmol/L (example: FPG 250 mg/dL = 13.9 mmol/L; thus, insulin dose would be 13 U daily)
  – 50% to 60% of the daily dose should be administered as basal insulin, with the remainder divided into mealtime bolus doses

Adjusting Basal Insulin Doses
• Monitor FPG and make adjustments as follows: if FPG (mean) over preceding 2 days is ________ mg/dL, then increase insulin dose by ________ U
  >180 8
  140–180 6
  120–140 4
  100–120 2
• If FPG <80 mg/dL for 3 consecutive days or ≥3 times per week, decrease basal insulin dose by 2 U

Mealtime Bolus

- **Supplemental insulin:** increase/decrease dose to bring premeal or bedtime glucose into desired range
  - 1 U insulin will change blood glucose by approximately 50 mg/dL for insulin-sensitive patients
- **Activity:** decrease dose to account for postprandial exercise
  - By 30% for exercise <1 hour
  - By 40% for exercise 1–2 hours
  - By 50% for exercise >2 hours
- **Food:** generally 1 U:15 g carbohydrate
  - May be 1:10 or 1:5 in insulin-resistant patients
  - May vary by time of day or type of food
- **Experience:** SMBG provides a way of learning what works

Mealtime bolus doses can be guided by the acronym SAFE.
- **Supplemental insulin:** increase or decrease dose as needed to bring preprandial or bedtime glucose levels to target
  - Most insulin-sensitive patients require 1 U insulin to change blood glucose by 50 mg/dL
  - Insulin-resistant individuals may require more insulin for comparable change
- **Activity:** adjust doses based on activity levels as shown
  - Remember that insulin dose may decrease as patient becomes more fit or loses weight
- **Food:** anticipated need for meal coverage is based on insulin-to-carbohydrate ratio
  - Insulin-sensitive individuals generally require 1 U insulin for each 15 g carbohydrates
  - Insulin-to-carbohydrate ratio may vary by time of day or with certain foods (eg, pizza)
  - Patient should be taught methods of carbohydrate counting
- **Experience:** SMBG provides valuable information regarding patient needs; adjustments should be made one at a time, in the following order:
  - Address persistent hypoglycemia
  - Address FPG to target range of 90–130 mg/dL
  - Bring preprandial into target range (90–130 mg/dL)
  - If A1c is still not met, adjust mealtime insulin or switch to rapid-acting insulin analog to reduce PPG to <180 mg/dL
  - Reminder: monitor for dawn phenomenon


Carbohydrate Counting

- Technique based on the concept that most meal-related glucose increase is due to the carbohydrate content of meals
- Patients count either
  - Servings of starches (milk, fruit, breads, sweets, and starchy vegetables)
  - Grams of “total carbohydrates” on food label
- Providers prescribe insulin-to-carbohydrate ratio
  - eg, 1 U/serving or 1 U/15 g
  - Typical dose is 2–10 U/serving in type 2 diabetes
- Titrate based on PPG control achieved


- Technique based on the concept that most PPG increase is due to the carbohydrate content of meals
- Patients count either by carbohydrate choices or by actual grams of carbohydrate
  - Servings of carbohydrates (milk, fruit, breads, sweets, and starchy vegetables)
  - Grams of total carbohydrates as listed on food label
- Providers prescribe insulin-to-carbohydrate ratio
  - eg, 1 U/serving or 1 U/15 g
    - More than one ratio is often required in the same patient
      - Influenced by time of day, degree of insulin resistance, and level of physical activity
  - Typical dose is 2–10 U/serving in type 2 diabetes
- Titrate based on PPG control achieved

P. C.—Patient Outcome

- Patient started on rapid-acting insulin prior to all meals, in addition to insulin detemir at bedtime
- Dietician and nurse educator consult to discuss insulin sensitivity measures and methods of carbohydrate counting
- Lisinopril increased to 20 mg
- Tingling in extremities decreased

- This patient’s case illustrates the natural history of type 2 DM, which is a progressive disease with declining β-cell function leading to the need for adjustments in treatment strategies to maintain glycemic control
Considerations for Basal-bolus Insulin Therapy

- Patient ability to participate in therapy
- Patient willingness to
  - Perform SMBG
  - Learn carbohydrate counting
  - Maintain close contact with physician
- Patient has no life-threatening illness and minimal end-stage complications
- Patient awareness of hypoglycemia
- Availability of team to support patient
Implementing Current Guidelines to Achieve Glycemic Control

- Detect and treat prediabetes
  - Delay or prevent progression to type 2 diabetes
  - Criteria for IFG: lowering diagnostic threshold from 6.1 to 5.6 mmol/L

- Achieve and maintain glycemic control via an uncompromising treat-to-target approach
  - FPG and PPG must be controlled

- Individualize treatment to meet each patient’s needs
  - Use oral agents or insulin as necessary
  - Improve adherence to therapy with ongoing nutrition and self-management education

IFG = impaired fasting glycemia.

Summary

In this program we have:

- Reviewed the pathophysiology of Type 2 Diabetes
- Identified the different therapeutic modalities available
- Explained the differences between various insulin preparations available and the pharmacodynamic properties
- Explored physiological insulin replacement
- Addressed some concerns for cardiovascular risk factor modifications