What’s New in Diabetes Treatment

Shiri Levy M.D.
Henry Ford Hospital
Senior Staff Physician
Service Chief, West Bloomfield Hospital
Endocrinology, Metabolism, Bone and Mineral Disorders

Disclosures

• None
Objectives

1) Increase awareness of new treatments
2) Learn about indications for use
3) Review effectiveness of therapy
Pre-Diabetes

• Impaired glucose tolerance (IGT): plasma glucose value of 140 to 199 mg/dL 2 hours after ingesting 75 g of glucose, and/or
• Impaired fasting glucose (IFG): fasting glucose value of 100 to 125 mg/dL
• A1C values between 5.5 and 6.4% (screening tool)
• FPG measurement or an oral glucose tolerance test (OGTT) should be used for definitive diagnosis

Diagnosis of Diabetes

• FBG concentration (after 8 or more hours of no caloric intake) ≥ 126 mg/dl, or
• Plasma glucose concentration of ≥ 200 mg/dL 2 hours after ingestion of a 75 g oral glucose in the morning after an overnight fast of at least 8 hours, or
• Symptoms of hyperglycemia (e.g., polyuria, polydipsia, polyphagia) and a random (casual, nonfasting) plasma glucose concentration ≥200 mg/dL, or
• A1C level ≥6.5%
Diagnosis of Diabetes

• Glucose criteria are preferred for the diagnosis of DM
• In all cases, the diagnosis should be confirmed on a separate day by repeating glucose or A1C testing
• When A1C is used for diagnosis, follow-up glucose testing should be done when possible to help manage DM.
Glycemic Treatment Goals

A less stringent glucose goal should be considered (A1C 7 to 8%) in patients with history of:

1) severe hypoglycemia
2) limited life expectancy
3) advanced renal disease or macrovascular complications
4) extensive comorbid conditions
5) long-standing DM in which the A1C goal has been difficult to attain despite intensive efforts (so long as the patient remains free of polydipsia, polyuria, polyphagia, and other hyperglycemia associated symptom

Antihyperglycemic Pharmacotherapy for DM2

• Pharmacotherapy for DM2 should be prescribed based on suitability for the individual patient’s characteristics
• Agents vary in their impact on FPG, PPG, weight, and insulin secretion or sensitivity, as well as the potential for hypoglycemia and other adverse effects
Antihyperglycemic Pharmacotherapy for DM2

- The initial choice of an agent involves comprehensive patient assessment including a glycemic profile obtained by self-monitoring of blood glucose and the patient’s A1C, weight, and presence of comorbidities

- It is imperative to minimize the risks of hypoglycemia and weight gain

Non-Insulin Pharmacological Therapy for Type 2 Diabetes

- 1) Biguanides
- 2) Sulfonylureas (SU)
- 3) Meglitinides
- 4) Alpha Glucosidase Inhibitors
- 5) Thiazolidinediones (TZD)
- 6) Dipeptidyl Peptidase-4 Inhibitors
- 7) GLP-1 Agonists
- 8) Sodium Glucose Cotransporter Inhibitor
- 9) Pramlintide
- 10) Bromocriptine
- 11) Colesevelam
DM2 and the Ominous Octet

- Decreases hepatic Glucose production
- Increases insulin sensitivity in muscle

Contraindications:
- Decreased renal function
- SCr > 1.4 women; SCr > 1.5 men
- eGFR < 30 mL/min
- Acute MI
- Iodine-contrast dye testing
- Hepatic Dysfunction

Biguanide (Metformin)
Biguanide (Metformin)

Efficacy: Lowers A1C ~ 1-2%

Benefits:
• “First-line” therapy for newly diagnosed individuals
• Can be use in “Pre-diabetes”
• Economical
• No hypoglycemia
• Some weight loss

Adverse Effects:
• GI disturbances
• Vitamin B12 deficiency
• Lactic Acidosis (low incidence)

Sulfonylureas
Secretagogues = stimulate insulin secretion by pancreatic β – cells

First generation
Chlorpropamide
Tolazamide
Tolbutamide

Second generation
Glimepiride
Glipizide
Glyburide
Sulfonylureas

Efficacy: Lowers A1C ~ 1 – 2 %

Benefits:
• Low cost, oral route
• Could use “Daily” dosing

Adverse Effects:
• Hypoglycemia
• Weight gain

Meglitinides

Secretagogues = stimulate insulin secretion by pancreatic β – cells

• Repaglinide (Prandin®)
• Nateglinide (Starlix®)

• It is different than the sulfonylureas due to a faster onset of action and shorter half-life
• Dose “BEFORE” meals 15 -30 min
• If skip meal = skip dose
**Meglitinides**

**Efficacy:** Lowers A1C ~ 0.5 – 1.5%

**Benefits:**
- Less hypoglycemia
- Dosing flexibility
- Good for patients with erratic schedules

**Adverse Effects:**
- Weight gain
- Hypoglycemia

**α - Glucosidase Inhibitors**

Inhibit the breakdown of complex carbohydrates in the intestines

- Acarbose (Precose®)
- Miglitol (Glyset®)
- Dose with “first bite of meal” -> decreases post-prandial blood sugar
α - Glucosidase Inhibitors

**Efficacy:** Lowers A1C ~ 0.5 – 1%

**Benefits:**
- Moderate reduction in post prandial glucose

**Adverse Effects:**
- Flatulence (70%)
- Diarrhea (30%)

Thiazolidinediones

Increase insulin sensitivity by “Peroxisome proliferator-activated receptor γ modulators

- Pioglitazone (Actos®)
- Rosiglitazone (Avandia®)
Thiazolidinediones

Efficacy: Lowers A1C ~ 0.6-2%

Benefits:
• Moderate fasting plasma glucose lowering.

Adverse Effects:
• Fluid retention, edema
• Bone fractures in females
• Bladder cancer
• Heart Failure

Insulin Is Decreased and Glucagon Is Increased in Patients With T2DM

CHO Meal

Glucagon

Glucose

Insulin

Incretin

- Group of metabolic hormones that stimulate a decrease in blood glucose levels
- They cause an increase in the amount of insulin released from pancreatic beta after eating
- They also slow the rate of absorption of nutrients into the blood stream by reducing gastric emptying
- They inhibit glucagon release from the alpha cells

GLP-1 vs DPP-4 Inhibitors—Understanding the Antidiabetic Actions of Incretin-based Therapies

- Food intake
- GLP-1 Promotes satiety and reduces appetite
- β-cell function
- Liver
- Glucagon reduces hepatic glucose output
- GLP-1 and DPP-4 inhibitors
- Excess glucose production
- α-cell
- Glucagon excess: Basal and postmeal
- Stomach
- Delays gastric emptying
- Glucose absorption

DPP-4 Inhibitors

- Inhibit Dipeptidyl Peptidase - 4 enzyme
- Prolongs the action of Glucagon-Like peptide (GLP-1)

- Sitagliptin (Januvia®)
- Saxagliptin (Onglyza®)
- Linagliptin (Tradjenta®)
- Alogliptin (Nesina®)

Efficacy: Lowers A1C ~ 0.6 – 1.2 %

Benefits:
- Weight neutral
- Well-tolerated, oral dosage form

Adverse Effects:
- Headache
- Nasopharyngitis
- Pancreatitis
- Lymphopenia (Saxagliptin)

Considerations:
- Patients with renal insufficiency will need dosage adjustment (except Linagliptin)
GLP-1 Actions in Peripheral Tissue

Cardioprotection
Cardiac output

Appetite

Gastric emptying

GLP-1

GLP-1

GLP-1

GLP-1

GLP-1

Insulin sensitivity

Insulin secretion

Glucagon secretion

Glucose production

Beta-cell apoptosis

Insulin biosynthesis

Beta-cell proliferation

Glucose production

Cardiac output

Appetite

Gastric emptying

GLP-1

GLP-1

GLP-1

GLP-1

GLP-1

Insulin sensitivity

Insulin secretion

Glucagon secretion


GLP-1 Agonists

Exenatide
• Byetta: 5 or 10 mcg pen – twice daily
• Bydureon: 2 mg extended-release – once weekly
Liraglutide (Victoza): Doses 0.6, 1.2, 1.8 mg -- once daily
Albiglutide (Tanzeum®) 30 mg or 50 mg pen – once weekly
Dulaglutide (Trulicity®)
GLP-1 Agonist

Efficacy: Lowers A1C 0.5 – 1.5%

Benefits
• Weight loss

Adverse effects
• Nausea/vomiting
• Pancreatitis
• Thyroid carcinoma

Considerations
• Expense
• CrCl < 30 mL/min - Exenatide not recommended

Amylin

Hormone cosecreted with insulin
• Slows gastric emptying
• Decreases postprandial glucagon
• Increases satiety
• Decreases food intake
Pramlintide acetate (Symlin®)

Synthetic analog of amylin

Efficacy: Lowers A1C 0.5 – 0.7%

Benefits:
- Slows gastric emptying
- Decreases postprandial glucagon
- Increases satiety / food intake

Adverse effects
- Nausea
- Hypoglycemia

Considerations
- Multiple injections

Sodium-Glucose Cotransporter Inhibitors

Inhibit sodium-glucose transport proteins (SGLT2) in the kidney
Inhibits reabsorption of glucose back into the bloodstream

Agents
- Canagliflozin (Invokana®)
- Dapagliflozin (FarxigaTM)
- Empagliflozin (Jardiance®)
SGLT-2 Inhibitors

Efficacy: Lowers A1C ~ 0.5 – 1.0%

Benefits
- Weight loss 2-3 Kg
- Lowers blood Pressure 3-5 mm Hg

Adverse Effects
- UTI infections
- Genital infections
- ↑ Hematocrit and Phosphorus
- Hypotension

Bromocriptine

Dopamine receptor agonist

Mechanism of action: act on the circadian neuronal activities in the hypothalamus, to reset an abnormally elevated hypothalamic drive for increased plasma glucose, free fatty acids, and triglycerides in insulin-resistant patients
Bromocriptine

Efficacy: Lowers A1C 0.5 – 0.6%

Dosing: Start 0.8 mg daily
- Titrate weekly by 1 tab to reach from 1.6 – 4.8 mg daily (2 to 6 tabs per day). Take with food within 2 hrs of waking in am

Adverse Reactions:
- Hypotension
- Hallucinations
- Psychotic episodes
- Vision problems
- Felling short of breath
- Swelling in ankles and feet

Colesevelam

Efficacy: Lowers A1C ~ 0.5%

Colesevelam (Welchol®)

- Mechanism of Action = Bile Acid sequestrant may exert glycemic effects
- Dosing 6 tabs daily or 3 tabs BID (supplied as 625 mg tabs) taken with meal + liquid
60 yo female with DM2 asks you about starting a GLP-1 therapy. She had a history of pancreatitis. What is the appropriate response?

1. Consider a class of agents other than GLP-1 RAs
2. Discuss current evidence regarding the potential risk of pancreatitis with GLP-1 RAs
3. Order an initial pancreatic enzyme series and continue monitoring over time
4. Write a prescription for a GLP-1 RA and digestive enzymes
Which of the following is a contraindication for some GLP-1 RAs?

1. CVD
2. History of MTC
3. History of severe hypoglycemia
4. Any degree of renal insufficiency
Which class of agents would be most likely to decrease A1C by >1% with weight loss?

1. DPP-4i
2. GLP-1 RA
3. SGLT2 inhibitor
4. Sulfonylureas
5. TZD

Which class of agents would be most likely to decrease A1C by >1% with weight loss?

1. DPP-4i
2. GLP-1 RA
3. SGLT2 inhibitor
4. Sulfonylureas
5. TZD
Which of the following is not a diagnosis of diabetes?

1. FBG concentration (after 8 or more hours of no caloric intake) ≥ 126 mg/dl
2. Plasma glucose concentration of ≥ 200 mg/dL 2 hours after ingestion of a 75 g oral glucose in the morning after an overnight fast of at least 8 hours
3. Symptoms of hyperglycemia (e.g., polyuria, polydipsia, polyphagia) and a random (casual, nonfasting) plasma glucose concentration ≥200 mg/dL, or
4. A1C level ≥5.7%

Which of the following is not a diagnosis of diabetes?

1. FBG concentration (after 8 or more hours of no caloric intake) ≥ 126 mg/dl
2. Plasma glucose concentration of ≥ 200 mg/dL 2 hours after ingestion of a 75 g oral glucose in the morning after an overnight fast of at least 8 hours
3. Symptoms of hyperglycemia (e.g., polyuria, polydipsia, polyphagia) and a random (casual, nonfasting) plasma glucose concentration ≥200 mg/dL, or
4. A1C level ≥5.7%