Hyperglycemia in Type 2 Diabetes

- Impaired insulin secretion
  - Sulfonylurea
  - Meglitinide
  - GLP-1 receptor agonists
  - DPP-4 inhibitors

- Increased glucagon secretion
  - GLP-1 receptor agonists
  - DPP-4 inhibitors
  - Amylin

- Increased hepatic glucose production
  - Metformin
  - Insulin
  - Thiazolidinediones

- Decreased incretin effect
  - Metformin
  - α-Glucosidase inhibitors
  - Colesevelam

- Neurotransmitter dysfunction
  - GLP-1 receptor agonists
  - Amylin
  - Bromocriptine

- Increased lipolysis and reduced glucose uptake
  - Thiazolidinediones

- Increased glucose reabsorption

- Decreased glucose uptake
  - Metformin
  - Insulin
  - Thiazolidinediones

References:
• **Normal Fuel Metabolism**
  
• **Five phases of fuel homeostasis** have been described

• **A. Phase I** is the fed state (0 to 3.9 hours after meal/food consumption), in which blood
  
  • glucose predominantly originates from an exogenous source.
  
  • The brain and other organs use some of the glucose that has been absorbed from
  
  • the gastrointestinal tract.
  
  • The remaining glucose is added to hepatic, muscle, adipose, and other tissue reservoirs.
  
  • Plasma insulin levels are high, glucagon levels are low, and triglyceride is synthesized
  
  • in liver and adipose tissue. Insulin inhibits breakdown of glycogen and
  
  • triglyceride reservoirs.
• **B Phase II** is the postabsorptive state (4 to 15.9 hours after food consumption), in which
• blood glucose originates from glycogen breakdown and hepatic gluconeogenesis.
• • Plasma insulin levels decrease and glucagon levels increase.
• • Energy storage ends in this phase and energy production begins.
• • Carbohydrate and lipid stores are mobilized. Hepatic glycogen breakdown provides
• glucose to the brain and other tissues. Blood glucose levels are maintained.
• • Adipocyte triglyceride begins to break down and free fatty acids (FFA) are released
• into the circulation and utilized by the liver and skeletal muscle as a primary energy
• source.
• • The brain continues to use glucose, provided mainly by gluconeogenesis (35%
• to 60%) because of its inability to use FFA as fuel.
• **Phase III** is the early starvation state (16 to 47.9 hours after food consumption),
• in which blood glucose originates from hepatic gluconeogenesis and glycogenolysis.
• • Gluconeogenesis continues to produce most of the hepatic glucose.
• • In this phase of starvation, lactate makes up half of the gluconeogenetic substrate.
• • Amino acids, specifically alanine, and glycerol are other major substrates.
• • Insulin secretion is markedly suppressed and counterregulatory hormone (eg, glucagon, cortisol, growth hormone, and epinephrine) secretion is stimulated.
• **D Phase IV** is the preliminary prolonged starvation state (48 hours to 23.9 days after food consumption), in which blood glucose originates from hepatic and renal gluconeogenesis.

• By 60 hours of starvation, gluconeogenesis provides more than 97% of hepatic glucose output. The need for gluconeogenesis is limited in order to conserve body protein by increased reliance of muscle and other tissues on FFA and ketone bodies.

• and a change from glucose to ketone bodies as fuel for the brain.

• Insulin secretion is markedly suppressed and counterregulatory hormone (eg, glucagon, cortisol, growth hormone, and epinephrine) secretion is stimulated.
• **E Phase V** is the secondary prolonged starvation state (24 to 40 days after food consumption),

• in which blood glucose originates from hepatic and renal gluconeogenesis,

• the same source as in Phase IV. In Phase V, the rate of glucose being used

• by the brain diminishes as does the rate of hepatic gluconeogenesis.
• Diagnostic Criteria for Diabetes Mellitus and Other
• Categories of Impaired Glucose Homeostasis
In 1997, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus updated the classification and diagnostic criteria for diabetes. Diabetes mellitus is diagnosed using any 1 of the 3 following methods and must be confirmed on a subsequent day.

- **A** Acute symptoms of diabetes plus casual plasma glucose concentration $\geq 200$ mg/dL (11.1 mmol/L).
- **B** Fasting plasma glucose $\geq 126$ mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.
- **C** Two-hour plasma glucose $\geq 200$ mg/dL (11.1 mmol/L) during a 75-g oral glucose tolerance test (OGTT).

Casual implies any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, polyphagia, and unexplained weight loss.
• **2 Impaired Fasting Glucose (IFG) is diagnosed when fasting glucose levels are ≥110 mg/dL (6.1 mmol/L) but <126 mg/dL (7.0 mmol/L). IFG represents a metabolic stage of impaired glucose homeostasis intermediate between normal and diabetes mellitus. IFG is not a category of diabetes mellitus.**

• **3 Impaired Glucose Tolerance (IGT) is diagnosed when 2-hour OGTT values are ≥140 mg/dL (7.0 mmol/L) but <200 mg/dL (11.1 mmol/L). IGT represents a metabolic stage of impaired glucose homeostasis intermediate between normal and diabetes mellitus. IGT is not a category of diabetes mellitus, but is associated with increased macrovascular disease.**
• **2** Insulin is a hormone essential for the use and storage of these nutrients. The action
• of insulin is both anticatabolic (prevents breakdown) and anabolic (promotes storage),
• and it facilitates cellular transport of nutrients.
• **A** Insulin suppresses hepatic glycogenolysis and gluconeogenesis and inhibits lipolysis
• and proteolysis. Insulin also stimulates glycogen synthesis and facilitates the transport
• of glucose into muscle cells.
• **B** The effects of insulin are balanced by the effects of the counterregulatory hormones:
• glucagon, growth hormone, cortisol, epinephrine, and norepinephrine
• Carbohydrate provides 4 kcal per gram.

In the metabolism of carbohydrate, insulin facilitates entry of glucose into cells, stimulates glycogen synthesis in liver and muscle cells, and increases triglyceride stores by facilitating the entry of glucose into adipose tissue and its conversion to triglycerides. Without insulin, glucose production by the liver (gluconeogenesis) is accelerated and in liver and muscle glycogenolysis occurs.
• Protein contributes 4 kcal per gram.

In the metabolism of protein, insulin lowers blood amino acids while reducing blood glucose levels, facilitates incorporation of amino acids into tissue protein, and decreases gluconeogenesis. Without adequate insulin, gluconeogenesis increases and proteolysis and amino acid release occurs in muscle.
• Fat contributes 9 kcal per gram.

In the metabolism of fat, insulin promotes lipogenesis by activating lipoprotein lipase, the enzyme that facilitates transport of triglycerides into adipose tissue for storage. Insulin also inhibits lipolysis and stimulates hepatic lipogenesis. Without adequate insulin, ketogenesis occurs in the liver, and lipolysis and fatty acid release occurs rapidly in adipose tissue, leading to excessive production of ketones and eventually ketoacidosis. Triglyceride levels also increase due to a decrease in cellular uptake of triglycerides.
hormones effects hypoglycemic actions of insulin:

• The primary counterregulatory hormones include

• A Glucagon (produced in the alpha cells of the pancreas)

• B Epinephrine

• C Norepinephrine

• D Growth hormone

• E Cortisol
The FDA has currently approved agent or agents within 12 classes of drugs for treatment of type 2 diabetes

Insulin
Biguanide: metformin (insulin sensitizer)
Sulfonylureas: first- and second-generation (insulin secretagogues)
Thiazolidinediones (glitazones): (insulin sensitizer)
D-Phenylalanine derivative: starlix (insulin secretagogues)
Benzoic acid derivative: prandin (insulin secretagogues)
Alpha-glucosidase inhibitors: precose/glyset (delay glucose absorption)
DDP-4 inhibitors
GLP-1 Agonists
Amylin analogue: symlin
SGLT2 inhibitors
Dopamine Agonists: Cycloset
Insulin initiate soon, not later

1. If the diabetes has been there for > 12-15 years;
2. Older people and African Americans;
3. Significant impairment of renal function;
4. The presence of coronary calcification;
5. The history of peripheral neuropathy and the findings of autonomic neuropathy.
• AACE: Why Physicians Delay the Start of Insulin in Type 2 Diabetes Patients

physicians felt that their patients would perceive the initiation of insulin as a failure to control their blood glucose. How they think their patients will react is the biggest barrier to initiating insulin." Education is important not only for the patient but for their primary care provider as well, the more experienced providers were not only aware of treatment guidelines, but were also more comfortable with using insulin in their patients. Providers who were less comfortable initiating insulin felt that more education was needed. More than half of the responding primary care physicians felt that the various forms of insulin created confusion for prescribing. But were also more comfortable with using insulin in their patients.
## Table 3.3. Comparison of Human Insulins and Analogs

<table>
<thead>
<tr>
<th>Insulin Preparations</th>
<th>Onset of Action</th>
<th>Peak</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro/Aspart</td>
<td>5-15 minutes</td>
<td>1-2 hours</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>Human Regular</td>
<td>30-60 minutes</td>
<td>2-4 hours</td>
<td>6-10 hours</td>
</tr>
<tr>
<td>Human NPH/Lente</td>
<td>1-2 hours</td>
<td>4-8 hours</td>
<td>10-20 hours</td>
</tr>
<tr>
<td>Human Ultralente</td>
<td>2-4 hours</td>
<td>Unpredictable</td>
<td>16-20 hours</td>
</tr>
<tr>
<td>Glargine</td>
<td>1-2 hours</td>
<td>Flat</td>
<td>~24 hours</td>
</tr>
</tbody>
</table>

*Note: The time course of action of any insulin may vary in the same individual. Because of this variation, time periods indicated here should be considered general guidelines only.*

*Source: Adapted from White JR Jr, et al.*
Figure 3.2. Time Action Profiles of Glargine vs NPH Insulin in Type 1 Diabetes

Source: Reprinted with permission from Lepore.\textsuperscript{15}
Figure 3.3. Time Action of Physiologic (Endogenous) Insulin*

B = breakfast, L = lunch, S = supper, HS = bedtime.

“Bolus” secretion: The biphasic release of insulin in response to food intake.
“Basal” secretion: The release of insulin to counteract ongoing hormonal or other glycemic influences.
• Biguanide: metformin (insulin sensitizer)

• First line for New ACP guideline
• Cr 1.4 for women, 1.5 for men
• Caution for heart failure
• Sulfonylureas: first- and second-generation (insulin secretagogues)
• Hypoglycemia
• Wt gain
• Renal dysfunction
• Treatment failure
• Caution for elderly
• Thiazolidinediones (glitazones): (insulin sensitizer)

  fluid retention and peripheral edema, and are associated with a 2-fold increase in risk of developing heart failure contraindicated in patients with New York Heart Association class III or IV heart failure also associated with 1.5- to 2.5-fold increased risk for bone fractures. Elevated hepatic enzymes
• Benzoic acid derivative: prandin (insulin secretagogues)
• Nonsulfonylurea, but share many pharmacologic actions and adverse effects of sulfonylurea
• Renal function
• GI side effects
• D-Phenylalanine derivative: starlix (insulin secretagogues)
• Decrease meal time glucose excursions
• Monotherapy
• No dose adjustment for elderly
Alpha-glucosidase inhibitors: precose/glyset (delay glucose absorption)

- Reduce postprandial blood glucose elevation
- Not associated with hypoglycemia
- GI side effect
• **DDP-4 inhibitors: 4 medications plus 7 combinations**

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of oral drugs for type 2 diabetes that inhibit the breakdown of glucagon-like peptide-1 (GLP-1) and increase the release of insulin in response to a meal.

In clinical practice, they do not cause weight gain and are weight neutral, with a very low incidence of hypoglycemia as a side effects.

Results of cardiovascular safety studies have not shown any indication of cardiovascular harm, with possible suggestion of cardiovascular benefit.
• GLP-1 Agonists
• Byetta SC BID/Bydureon SCwkly
• Victoza SQ daily

Endogenous GLP-1 is released from the gut in response to food intake. It stimulates insulin secretion and promotes beta-cell proliferation. GLP-1 also inhibits glucagon secretion, gastric emptying, food intake, and weight gain. Increasing GLP-1 activity offers multiple potential benefits
• Amylin analogue: symlin

• Amylin is a hormone secreted by the pancreatic beta cells in response to hyperglycemia, the main mechanism of amylin is to inhibit gastric emptying and to a lesser extent, suppression of glucagon secretion

• Symlin is a synthetic version of human amylin
• SGLT2 inhibitors

  • Improve glycemic control by eliminating excess glucose via the urine
  • Assist weight control
  • Act independently of insulin
  • Low risk of hypoglycemia
  • Compatible with other diabetes medications
  • Small decrease in blood pressure
Dopamine Agonists: Cycloset 0.8mg
Glucagon

- for severe hypoglycemia
- Raise blood glucose levels by accelerating hepatic glycogenolysis and hepatic gluconeogenesis
- Glucagon is effective if adequate glycogen (stored glucose) is available, but may not be beneficial in patients with inadequate glycogen stores (e.g., pt with ETOH hepatic disease, starvation, adrenal insufficiency, or chronic hypoglycemia)
- Can be given IM, IV, or SQ
  - unconscious or uncooperative
  - can not take oral fluids
- Blood glucose response usually occurs in 5-20 mins, an addition dose may added if response is insufficient
- Common side effects: N/V
- Instruct pt to eat snack, may need to be repeated because glycogen reserves can take 8-12hrs to be replenished
• ADA/EASD Issue New Hyperglycemia Management Guidelines 2012

• Glycemic targets and treatments to lower glucose must be individualized according to specific patient characteristics.
• The mainstay of any type 2 diabetes treatment program is still diet, exercise, and education.
• Metformin is the preferred first-line drug, in the absence of contraindications.
• Data are limited regarding use of agents other than metformin. A reasonable approach is combination therapy with 1 to 2 additional oral or injectable agents, with the goal of minimizing side effects to the extent possible.
• To maintain glycemic control, many patients will ultimately need insulin monotherapy or in combination with other medications.
• Whenever possible, the patient should participate in all treatment decisions, focusing on their preferences, needs, and values.
• A major treatment goal must be comprehensive cardiovascular risk reduction.
AACE Releases New Comprehensive Diabetes Management Algorithm

new comprehensive diabetes management algorithm created to guide primary care physicians, endocrinologists and other health care professionals in the treatment of prediabetes and type 2 diabetes mellitus (T2DM) patients.

Management of diabetes and co-existing diseases or disorders in the prediabetic phase of disease.

A hierarchy of steps for the management of high blood sugar control using an approach that balances age and comorbidities while minimizing the adverse effects of hypoglycemia and weight gain.

Complications-centric treatment of the overweight or obese patient, as opposed to a body mass index (BMI)-centric approach, including medical and surgical treatments for greater weight loss.

Management of cardiovascular disease risk factors, hypertension and hyperlipidemia (high lipid levels) in those patients with prediabetes or T2DM
• Also, while suggesting an blood sugar goal of less than 6.5% A1c as optimal for most diabetes patients if it can be achieved in a safe manner, the algorithm recommends the target be individualized based on numerous factors such as age, comorbid conditions, duration of diabetes, risk of hypoglycemia, patient motivation and adherence, and life expectancy. Higher targets may be appropriate for some individuals and may change for a given individual over time.
• Diabetes management for elderly/longterm patient

• framework" for consideration of treatment goals for glycemia, blood pressure, and dyslipidemia among adults aged 65 years and older with diabetes, based on 3 broad groupings
1. healthy, with few coexisting chronic conditions and intact cognitive and functional status;
2. complex/intermediate, with multiple coexisting chronic illnesses or 2 or more impairments in activities of daily living or mild to moderate cognitive impairment
3. very complex/poor health, in long-term care or with end-stage chronic illnesses or moderate to severe cognitive impairment or with 2 or more activities of daily living dependencies.
Diabetes management: Illness
During illness and surgery, there is an increase in the secretion of counterregulatory hormones, including cortisol, catecholamines (epinephrine and norepinephrine), growth hormone, and glucagon.

A Catecholamines cause an increase in heart rate, increase blood pressure, and dilate the bronchi to maximize the amount of oxygen that is supplied to the body. Blood is diverted from the vulnerable surface of the body to the core to supply the vital organs with essential oxygen. Since blood is diverted from the skin and subcutaneous fat, injected insulin may not be absorbed.

B Epinephrine decreases the uptake of glucose by the muscle tissue and inhibits the release of endogenous insulin.
• **Guidelines for Sick-Day Management**
  • Maintain adequate hydration because of the risk of dehydration from decreased fluid intake, polyuria, vomiting, diarrhea, and evaporative losses from fever
  • Increase the frequency of blood glucose monitoring and initiate ketone monitoring during suspected or acute illness.
  • Adjust medications during illness.
  • Substitute liquids or soft foods if patients are unable to tolerate usual foods at meal times because of nausea or anorexia.
  • Teach patients when to call their healthcare provider.