COURSE OBJECTIVES

• Review the function of insulin.
• Review currently available forms of insulin.
• Review current ADA guidelines for initiating insulin therapy.
• Review techniques for initiating and titrating insulin therapy.
HOW DOES INSULIN WORK?

• Insulin is a 51-amino acid peptide hormone derived from the precursor proinsulin.
• It is synthesized within the beta cells of the pancreas, and secreted in a dose-dependent response to glucose entry into the beta cells.
• Insulin binds to the insulin receptor, located on the target cells’ plasma membrane.
• This leads to a conformational change within the receptor structure, and a complicated signalling pathway of phosphorylation of multiple tyrosine residues upon signalling molecules.
• The end result of the pathway is the translocation of the GLUT-4 receptor onto the plasma membrane, which leads to increased glucose disposal.
WHAT IS TREATED WITH INSULIN?

• Type 1 diabetes
  • Autoimmune disease which causes the selective destruction of the insulin-producing cells of the pancreas (beta cells), which then leads to insulin deficiency.

• Type II diabetes
  • Disease of insulin resistance, in which pancreatic overproduction of insulin is not sufficient to maintain normoglycemia.

• Gestational diabetes
  • Diagnosed between 24 and 28 weeks’ gestation, and caused by increased insulin resistance from placental hormone production.
The acronyms “IDDM” and “NIDDM” were adopted by the World Health Organization in 1979.

- Insulin-dependent diabetes mellitus
- Non-insulin-dependent diabetes mellitus

The use of these acronyms was discarded in 1999 by the ADA, due to the fact that insulin use is common to both types of diabetes.

Correct terminology:

- Type I diabetes (insulin deficiency)
- Type II diabetes (insulin resistance)
ORIGIN OF THERAPEUTIC INSULIN

- It had been long recognized that pancreatic destruction was responsible for diabetes mellitus, but finding the key component of the pancreas was problematic.

- Animal insulin was first isolated and purified in 1922.

- In 1923, Dr. Frederick Banting shared the Nobel Prize for physiology with Dr. James Macleod for the discovery of insulin.
TYPES OF INSULIN: 2011

- Neutral protamine hagedorn (NPH)
- Regular human insulin
  - U-100 insulin
  - (100 units/mL)
  - U-500 insulin
  - (500 units/mL)
- Rapid-acting insulin analogs
  - Lispro
  - Aspart
  - Glulisine
- Long-acting insulin analogs
  - Glargine
  - Detemir
- Premixed insulin combinations:
  - Intermediate-action insulin with short-acting insulin, 70%/30%
INSULIN DEPOSITION AND ABSORPTION

- Insulin proteins self-associate in solution.
- Insulin can form dimers, or larger aggregates (e.g. hexamers)
- Smaller protein aggregates have a shorter onset to peak effect, and a shorter duration of action.
- Rapid-acting insulin analogs have 2 altered amino acids, as compared to human insulin, to prevent dimerization.
- Long-acting insulin analogs form hexamers in solution, and thus have prolonged absorption.
  - Protamine and zinc components of synthetic insulin facilitate aggregation and thus prolong absorption.
Figure 6. Representation of insulin self association in solution. Insulin dimers are non-covalently linked in a β-pleated sheet configuration. Insulin hexamer formation requires the presence of zinc and insulin dimers.
The onset and duration of action of insulins help the prescriber choose the best program for the patient. A rapid-acting insulin, for example, would be best used at mealtimes.
INHALED INSULIN (EXUBERA)

- Inhaled insulin was pulled from the market voluntarily in October 2007.
- This was due to a lack of patient interest, and enthusiasm by physicians.
- Long-term safety concerns persisted regarding its effect on pulmonary function and ability to be used in patients with pulmonary disease.
- Administration and dosing were difficult.
- Other pharmaceutical companies have forms of inhaled insulin currently in development.
WHEN IS INSULIN INDICATED?

- When the diagnosis of type 1 diabetes is secure.
- When oral agents have failed to achieve an A1c of <7% in a type II diabetic.
- All pregnant women with diabetes documented prior to pregnancy.
- When fasting glucoses >120 mg/dL and/or postprandial glucoses >180 mg/dL in the hospitalized diabetic patient.
- When patients are admitted for life-threatening hyperglycemia.
- When previously well-controlled patients develop severe hyperglycemia due to exacerbating factors.
EXACERBATING FACTORS

• Hyperglycemia from acute illness results from many exacerbating factors, and insulin may be required when these are present:

  Immobility
  • Downregulation of muscle GLUT-4 receptors ⇒ decreased glucose disposal.
  • Increased catecholamine production
    • Increased gluconeogenesis ⇒ sustained hyperglycemia.

• Glucotoxicity
  • Hyperglycemia ⇒ impaired β-cell function.

• Medications
  • Corticosteroids
  • Cyclosporine
  • Atypical antipsychotics
  • Niacin
  • Pentamidine
  • Tacrolimus

Williams Textbook of Endocrinology, 10th ed. Poitout and Robertson, Endocrinology 143(2), 2002
However, initiation of insulin therapy, even when it is clearly indicated, is sadly often delayed.

According to one study of 7200 DM-2 patients, the average patient had:

- HbA$_{1c}$ >8% for 5 years after diagnosis until starting insulin, and
- HbA$_{1c}$ of >7.0% for about 10 years.

U.S. ATTITUDES TOWARD INSULIN

- According to the DAWN study, which assessed provider attitudes in different countries toward the initiation and usage of insulin, providers in the US were the third-most likely to delay insulin treatment.

WHY Aren’t Patients Started on Insulin?

- Patient perception of insulin administration.
- Lack of physician comfort with initiation of insulin.
- Aversion to being “the bad guy.”
- Lack of support staff for insulin teaching.
- Usage of insulin treatment as a threat or punishment.
BENEFITS OF INSULIN THERAPY

- Insulin is anti-hyperglycemic.
- It promotes wound healing.
- It has anti-inflammatory effects independent of its anti-hyperglycemic functions, via inhibition of CRP and PAI-1 production.
- It increases production of nitric oxide synthase, leading to vasodilation.
- It prevents platelet aggregation via inhibition of the P2Y12 pathway.

ADVERSE EFFECTS OF INSULIN THERAPY

- Hypoglycemia
- Weight gain
- Reversal of glucosuria and increased storage of glucose intake as adipose.
- Increased dietary indiscretions due to ability to control glucoses with adjustments in insulin doses.
- Treatment of frequent hypoglycemia (consuming calories which otherwise wouldn’t be consumed).
- Lipohypertrophy
- Increased focal fat deposition at the site of frequent insulin injections
- Insulin allergy (rare, <5% of patients)
BENEFITS OF GLYCEMIC CONTROL IN THE INPATIENT SETTING

- Improved hospital outcomes have been documented in the following settings, after implementing measures to control hyperglycemia as an inpatient:
  - Following coronary artery bypass grafting
  - One year following acute myocardial infarction
  - SICU patients
  - MICU patients
  - Inpatients admitted for management of COPD exacerbation
BENEFITS OF GLYCEMIC CONTROL IN THE OUTPATIENT SETTING

• More stringent glycemic control (HbA1c <7.0%) in outpatients has been shown to reduce:
  • The onset and progression of microvascular complications – DCCT/EDIC Trial.
  • Macrovascular complications – UKPDS trial.
The ADA has published practice guidelines for the pharmacologic treatment of type II diabetes.

The guidelines are divided into 2 tiers:

- **Tier One**: well-validated therapies, supported by strong evidence in the medical literature.
- **Tier Two**: less well-validated therapies, supported by practice experience and smaller studies.
ADA 2011 ALGORITHM

Tier 1: Well-validated core therapies

At diagnosis:
Lifestyle + Metformin

Lifestyle + Metformin + Basal insulin

Lifestyle + Metformin + Sulfonylurea

Lifestyle + Metformin + Intensive insulin

STEP 1

STEP 2

STEP 3

Tier 2: Less well-validated therapies

Lifestyle + Metformin + Pioglitazone
- No hypoglycemia
- Edema/CHF
- Bone loss

Lifestyle + Metformin + GLP-1 agonist
- No hypoglycemia
- Weight loss
- Nausea/vomiting

Lifestyle + Metformin + Pioglitazone + Sulfonylurea

Lifestyle + Metformin + Basal insulin
A TALE OF TWO TIERS

- The two tiers have the first-line treatment for type II diabetes in common:
  - Lifestyle changes + metformin therapy.
- The two tiers differ upon therapy choices following a failure of the first-line treatment:
  - Tier One: LC + MTF + sulfonylurea or basal insulin
  - Tier Two: LC + MTF + other oral agents in combination +/- basal insulin
- When oral agents fail, insulin therapy is indicated.
- When basal insulin + oral agents fail, intensification of the insulin program is required.
COMMON INSULIN PROGRAMS

• Basal (long-acting) insulin + oral agents

• Basal insulin + bolus (short-acting) insulin at mealtimes

• Split-mix insulin
  • Predetermined doses of combination insulin, twice daily

• Any insulin program that involves multiple daily injections also requires that patients check their blood glucoses at least 3 times per day.
  • Improves patient safety
  • Prevents hypoglycemia
  • Improves accuracy of dose.
INITIATION OF BASAL INSULIN

• If a patient has failed oral agents, and has significant fasting hyperglycemia, initiating basal insulin while continuing oral agents is reasonable way to start insulin.

• The basal insulin dose can be started low (e.g. 10 units), and the patient can be instructed to increase the dose by 3-5 units every week until goal fasting glucoses have been achieved.

• If goal fasting glucoses have been achieved, but the patient’s HbA1c remains >7.0%, mealtime insulin is indicated.
**BASAL-BOLUS PROGRAM**

- The basal-bolus program is a method of administering insulin such that:
  - Long-acting insulin is active at all times of the day, specifically designed to treat fasting and between-meal hyperglycemia.
    - Glargine
    - Detemir
    - NPH
  - Works primarily to treat hyperglycemia caused by insulin resistance at the hepatic level.
  - It has been the standard of care for type 1 diabetes for years, recently shown to result in significantly better glucose control for type 2 diabetics, as well.

BASAL-BOLUS PROGRAM

• The bolus form of insulin is administered at mealtimes.
• A bolus insulin needs to have:
  • Rapid onset of action
  • Short duration of action
• The sole purpose of bolus insulin to prevent postprandial hyperglycemia.

• Encompasses two concepts:
  • Nutritional insulin
  • Correctional insulin

• Typical mealtime insulins:
  • Aspart
  • Lispro
  • Glulisine
  • Regular human insulin

The ideal mealtime bolus is administered BEFORE the meal begins.
NUTRITIONAL VS. CORRECTIONAL INSULIN

- **Nutritional insulin**: pre-meal insulin given to prevent hyperglycemia caused by ingested carbohydrate.

- **Correctional insulin**: insulin given to correct pre-existing hyperglycemia going into the meal.

- To be as precise as possible in calculating a bolus dose, both mealtime carbohydrate and premeal blood sugar need to be taken into account in order to prevent both postprandial hypo- and hyperglycemia.
DOSE DETERMINATION

• To intensify the program of a patient already on insulin, calculations can be made using his current total daily insulin consumption to determine his nutritional and correctional insulin doses.

• If a patient is not yet on insulin, the patient’s body weight can be used to predict total daily insulin consumption, and the same calculations can be made.
CALCULATION OF NUTRITIONAL INSULIN NEEDS

• Rule of 500:
  • 500 / total daily insulin =
    • number of carbohydrate grams requiring 1 unit of insulin to prevent hyperglycemia
  • Example: 500/100 units =
    • 1 unit of insulin for every 5 g of ingested carbohydrate

  • This patient would be instructed to take 1 unit of mealtime insulin for every 5 grams of planned carbohydrate in the meal.

  • This total is then added to the amount of correctional insulin required, which is derived from a sliding scale.

Walsh, J. *Pumping Insulin* 4th ed.
CALCULATION OF CORRECTIONAL INSULIN NEEDS

• Rule of 1800
  • calculation of correctional insulin needs:
  • 1800 / total daily insulin =
    • number of mg/dL decrease per unit of insulin given
  • Example: 1800/100 units = 1 unit of insulin is predicted to lower BG by 18 mg/dL

• The calculated nutritional + correctional dose equals the total mealtime dose.
• In some cases, correctional doses are not required, but nutritional doses are almost always necessary.
• In other words, a mealtime sliding scale should NEVER begin with zero!

Walsh, J. *Pumping Insulin* 4th ed.
Mr. Smith currently takes 75 units per day of insulin. He does not use a formal mealtime dosing algorithm, and because of frequent postmeal hypoglycemia, would like to be more accurate with insulin doses.

Based on his total daily use of 75 units, his nutritional insulin requirements would be:
- $500 \div 75 \approx 7$
- He will take 1 unit for every 7 grams of carbohydrate.

His correctional insulin requirements would be:
- $1800 \div 75 \approx 25$
- 1 unit of insulin is estimated to decrease his blood glucose by 25 mg/dL.
EXAMPLE CONTINUED…

- It is often easier for patients to be given a sliding scale, custom-built to accommodate their own insulin requirements and resistance, based on correctional insulin calculations.

- Below is an example of what would be provided to Mr. Smith, although he would be advised that his scale does not stop at 275 mg/dL.

<table>
<thead>
<tr>
<th>Blood glucose</th>
<th>Insulin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 125</td>
<td>0 units</td>
</tr>
<tr>
<td>126-150</td>
<td>1 unit</td>
</tr>
<tr>
<td>151-175</td>
<td>2 units</td>
</tr>
<tr>
<td>176-200</td>
<td>3 units</td>
</tr>
<tr>
<td>201-225</td>
<td>4 units</td>
</tr>
<tr>
<td>226-250</td>
<td>5 units</td>
</tr>
<tr>
<td>251-275</td>
<td>6 units</td>
</tr>
</tbody>
</table>
PUTTING IT ALL TOGETHER

• If Mr. Smith plans to consume 50 grams of carbohydrate at dinner:

• $50 / 7 \approx 7$ units of nutritional insulin.

• His measured blood glucose is 245 mg/dL, which according to his correctional scale requires 5 units to correct.

• $7 + 5 = 12$ total units of mealtime insulin.
There are times when patients are unable or unwilling to count carbohydrate grams when dosing mealtime insulin.

These patients should be informed that not doing so can lead to inaccurate mealtime dosing, loss of flexibility in adjusting insulin at mealtimes, and postmeal hypoglycemia.

These patients can be given a sliding scale, built based on their insulin requirements, but with a starting number that represents the estimated amount of nutritional insulin required at every meal.
A sliding scale that incorporates a standard nutritional dose of insulin, without variation, plus correctional insulin would look like this (using the previous example of Mr. Smith).

<table>
<thead>
<tr>
<th>Blood glucose</th>
<th>Insulin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 125</td>
<td>7 units</td>
</tr>
<tr>
<td>126-150</td>
<td>8 units</td>
</tr>
<tr>
<td>151-175</td>
<td>9 units</td>
</tr>
<tr>
<td>176-200</td>
<td>10 units</td>
</tr>
<tr>
<td>201-225</td>
<td>11 units</td>
</tr>
<tr>
<td>226-250</td>
<td>12 units</td>
</tr>
<tr>
<td>251-275</td>
<td>13 units</td>
</tr>
</tbody>
</table>
ADJUSTING INSULINS

- The nutritional dose needs to be adjusted if significant hyper- or hypoglycemia is noted following a meal that was only covered with nutritional insulin.

- If hyperglycemia persists throughout the day, then the correctional sliding scale level should be increased.

- As the patient consumes larger amounts of total daily insulin, the nutritional and correctional doses can be recalculated periodically to adjust the dosing parameters given to the patient.
• Mr. Smith returns to clinic, reporting that his fasting glucoses are now under excellent control, but that his premeal blood glucoses range from 180-250 mg/dL.

• His total daily insulin consumption is 90 units.
  • $500 \div 90 \approx 1$ unit for 5 grams of carbohydrate
  • $1800 \div 90 \approx 1$ unit to lower glucose 20 mg/dL.

• His dosing instructions should be rewritten accordingly.
STARTING INSULIN DE NOVO

• To calculate doses using body weight:
  – Take the patient’s body weight in kg, and multiply by 0.5:
    • Ex: 100 kg x 0.5 = 50
  – This represents the patient’s estimated total daily insulin requirement (NOT accounting for insulin resistance).
  – 50% of the daily insulin requirement should be provided in basal form, and 50% in bolus, or total mealtime form.
    • Ex: 50 units = 25 units of basal, ≈ 25 units of bolus (total)
To determine nutritional insulin:
- 500/50 = 1 unit for 10 grams of carbohydrate

To determine appropriate correctional insulin:
- 1800/50 = 35; 1 unit will lower blood glucose 35 mg/dL.

For patients with significant insulin resistance, these parameters will likely require increases after insulin is started.
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