• I am disclosing the following relationship or role with the following organization:

• Speaker’s Bureau – Novo Nordisk
Insulin Update 2019 Objectives

• Illustrate the evolution of insulin products used in the treatment of T1DM and T2DM
• Explain the concepts behind treatment strategies with insulin
• Discuss blood glucose changes and appropriate management responses in patients with T1DM and T2DM
Patient groups with diabetes

• Type 1: autoimmune beta cell destruction
• Type 2: progressive loss of Beta cell insulin secretion with a background of insulin resistance
• Gestational: diagnosed in 2\textsuperscript{nd} or 3\textsuperscript{rd} trimester
• Monogenic diabetes syndromes (e.g. neonatal diabetes, maturity onset diabetes in the young [MODY]); diabetes syndromes related to cystic fibrosis or pancreatitis; drug induced diabetes
Relationship of HbA₁c to Risk of Microvascular Complications

Relative Risk

Retinopathy
Nephropathy
Neuropathy
Microalbuminuria

HbA₁c (%) 6 7 8 9 10 11 12

Cardiovascular Risk
Mortality After MI Reduced by Insulin Therapy in the DIGAMI Study

All Subjects (N = 620)
Risk reduction (28%)  
\[ P = .011 \]

Years of Follow-up

Low-risk and Insulin-Naive (N = 272)
Risk reduction (51%)  
\[ P = .0004 \]

IV Insulin 48 hours, then 4 injections daily

Malmberg et al. *BMJ*  
1997;314:1512-5
Physiologic Insulin Secretion: 24-Hour Profile

Insulin (µU/mL)

Basal insulin

Breakfast  Lunch  Dinner

Glucose (mg/dL)

Basal glucose

Time of Day

7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 AM  PM
Progression of Type 1 Diabetes

Adapted from: Atkinson. Lancet. 2002;358:221-229.
Natural History of Type 2 Diabetes

Adapted from International Diabetes Center (IDC). Minneapolis, MN.
Type 2 Diabetes: Two Principal Defects

- Insulin resistance
- β-cell dysfunction/failure

Genes

± Environment

IGT

Glucose Toxicity

Type 2 diabetes

Glucose Toxicity

Reaven GM. *Physiol Rev.* 1995;75:473-486
Reaven GM. *Diabetes/Metabol Rev.* 1993;9(Suppl 1):5S-12S;
Insulin Structure

A - CHAIN

B - CHAIN
Action Profiles of Injectable Insulins

- Glulisine, aspart, lispro 4–6 hours
- Regular 6–8 hours
- NPH 12–20 hours
- Basal insulin: glargine, detemir

Plasma Insulin Levels vs. Hours
Intrasubject Variability (GIR) With NPH Insulin

The discovery of insulin (Toronto 1921)


James B. Collip (1892-1965)  Marjorie (?)
The Miracle of Insulin

Patient J.L., December 15, 1922

February 15, 1923
Famous people with diabetes
The person most famous for having diabetes...
Physiological Serum Insulin Secretion Profile

![Graph showing physiological serum insulin secretion profile with peaks at breakfast, lunch, and dinner times.](image)
Plasma insulin

Ideal Basal/Bolus Insulin Absorption Pattern

Breakfast  Lunch  Dinner

4:00  8:00  12:00  16:00  20:00  24:00  4:00  8:00

Time
Primary Structure of Lys(B28), Pro(B29)-Insulin

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**Insulin**

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Primary Structure of Asp(B28)-Insulin

Insulin: Gly, Glu, Phe, Tyr, Thr, Pro, Lys, Thr

Aspart: Gly, Glu, Phe, Tyr, Thr, Asp, Lys, Thr
Modified Human Insulin

Glulisine:
Replacement of asparagine B3 with lysine and lysine B29 with glutamic acid

Substitutions favor rapid dissociation after SC injection
Basal vs Mealtime Hyperglycemia in Diabetes

Δ AUC from normal basal >1875 mgm/dL·hr; Est HbA1c >8.7%

Basal vs Mealtime Hyperglycemia in Diabetes

When Basal Corrected

Δ AUC from normal basal 900 mgm/dL·hr; Est HbA1c 7.2%
When Mealtime Hyperglycemia Corrected

Basal vs Mealtime Hyperglycemia in Diabetes

Δ AUC from normal basal 1425 mg/dL·hr; Est HbA1c 7.9
When Both Basal & Mealtime Hyperglycemia Corrected

Basal vs Mealtime Hyperglycemia in Diabetes

$\Delta$ AUC from normal basal 225 mgm/dL·hr; Est HbA1c 6.4%
Classical “Split-mixed” Treatment Program

Plasma insulin

Breakfast  Lunch  Dinner

4:00  8:00  12:00  16:00  20:00  24:00  4:00  8:00

REG  REG  NPH  NPH

Classical “Split-mixed” Treatment Program

Time
“Split-mixed” Program with Bedtime Intermediate Insulin

- Breakfast
- Lunch
- Dinner

Plasma insulin

- REG
- NPH

Time

4:00  8:00  12:00  16:00  20:00  24:00  4:00  8:00
Basal/Bolus Insulin Absorption Pattern Standard Insulin Preparations
Basal/Bolus Treatment Program with Rapid-acting and Long-acting Analogs

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<tr>
<th>Time</th>
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<tr>
<td>4:00</td>
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<td>8:00</td>
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<td>12:00</td>
<td>Dinner</td>
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Plasma insulin

- Aspart or Lispro
- Aspart or Lispro
- Aspart or Lispro
- Aspart or Lispro

Basal insulin

Graph showing the plasma insulin levels at different times of the day with breakfast, lunch, and dinner times indicated.
Variable Basal Rate: CSII Program

Plasma insulin

Breakfast | Lunch | Dinner
---|---|---
Bolus | Bolus | Bolus

Basal infusion
Many individuals with type 2 diabetes may require mealtime bolus insulin dosing in addition to basal insulin. Rapid acting analogs are preferred due to their prompt onset of action after dosing.

• Diabetes Care 2018;41(suppl. 1);S83

Meta-analyses of trials comparing insulin analogs with human regular insulin in T2DM have not reported important differences in A1c or hypoglycemia

• Diabetes Care 2019;42 (suppl. 1)599
insulin human inhalation powder
Insulin human inhalation powder

- Rapid acting insulin approved for adults with DM
- Adsorbed to carrier particles
- Peak concentration in 12-15 minutes, peak glucose lowering at one hour
- Carrier particles not metabolized, eliminated unchanged
Insulin human inhalation powder

- Added to basal insulin or oral agents
- Cough
- Possible acute bronchospasm (avoid in chronic lung disease)
- Not for smokers or those who recently stopped
- Decline in FEV1 over time (baseline spirometry, 6 months then annual)
- 2 cases of lung cancer in clinical trials
- Start with 4 or 8 units dose, 24 units max per inhaled dose
- Replace inhaler every 15 days
insulin aspart injection
Insulin aspart (newest version)

- Proline substituted with aspartic acid at B28 position plus niacinamide added to promote faster onset of initial absorption
- Onset 16-20 minutes, peak effect 90-133 minutes
- Can be give SQ at start of meal or after start meal or by IV infusion
- Usually used in combination with basal insulin
Insulin Lispro biosimilar
U-500 insulin R insulin

- Insulin resistance patients who need > 200 units/day of U-100
- High concentration results in delayed absorption
- Onset at 30 minutes, peak 1-3 hours like regular insulin
- Q8h vs. Q24h dosing may depend on variability of blood flow at injection site and sensitivity of insulin receptors
- Usually two or three injections per day
U-500 insulin R insulin

• Can be used in a pump for insulin resistant patients but 5X concentration must be dose adjusted for the pump (careful!)
• All other insulin preps should be discontinued when U-500 started; oral agents OK
• Dosing adjustment strategy similar to NPH
• Caution regarding EHR drop down screens
• Store U-500 away from other insulin products
Insulin glargine
Insulin glargine

• Basal insulin
• Asparagine substituted to glycine, 2 arginines added at B30 position
• Buffered to pH of 4 in vial or syringe
• Forms microprecipitates when injected into the subcutaneous space
• Slow insulin absorption from there
• Some 1x/day dose, some 2x/day dose
• Side effects
• Dose
• Stability 28 days after open
Insulin Glargine Structure

- Asparagine at position A21 replaced by glycine
  - Provides stability
- Addition of 2 arginines at the C-terminus of the B chain
  - Soluble at slightly acidic pH
Figure 3. Mechanism of action of insulin glargine. Glargine, which has an acidic pH, is injected into subcutaneous space with normal pH, where it forms microprecipitates. Microprecipitates dissociate to hexamers, dimers, and finally, to monomers, which are absorbed across the capillaries.

Adapted from Kramer W. Exp Clin Endocrinol Diabetes 1999;107(Suppl 2): P42.
Intra-subject Variability
Insulin Glargine

Scholtz et al. *Diabetes* 1999;48(suppl 1):A97. Abst 416; Study 1012
Insulin glargine injection biosimilar
Insulin glargine biosimilar

• Recombinant human insulin analog with same amino acid sequence as the originator insulin glargine
Insulin Glargine U300
Insulin glargine U300

• Soluble, (clear) and buffered to pH of 4
• Smaller surface area exposed with 300unit/ml product compared to 100 unit/ml product
• Re-dissolution is reduced, prolonged and consistent effect
• Onset 6 hours, peak 12-16 hours, half-life 19 hours
• May need 5 days treatment to see maximum effect
• May have insufficient effect in first 24 hours of use
• 300 units/ml (expect to need 10% more units compared to insulin glargine U100 dose)
Figure 1—INS, GIR, and blood glucose profiles after multiple doses in steady state. Steady-state profiles of (A) mean INS (LLOQ = 5.02 units/mL), (B) smoothed (LOESS factor 0.15) body-weight-standardized GIR, and (C) smoothed (LOESS factor 0.15) biosensor measured blood glucose, with threshold of blood glucose control ≈118 mg/dL. All data shown from cohort 1: Gla-100 0.4 units/kg^{-1} versus Gla-300 0.4 units/kg^{-1}. BG, blood glucose.
Insulin detemir
Insulin detmir

- Threonine omitted from B30 and 14 member fatty acid attached at B29
- Reversible binding of free fatty acid to albumin
- Maximum concentration 6-8 hours after administration, half-life 5-7 hours
- T2DM insulin naïve dose: 0.1-0.2 units/kg once daily
Timing and variability of intermediate insulins
Insulin degludec
Insulin degludec

• Ultra-long acting insulin
• Last amino acid on B chain omitted, dicarboxylic acid coupled by glutamic acid spacer at B29
• Forms multi-hexamers with zinc core
• Some degree of albumin binding
• Half life 25 hours, glucose lowering effect for 42 hours
• Less clinical hypoglycemia than glargine
• Once daily any time of day
Insulin degludec

- Ultra-long acting insulin
- Last amino acid on B chain omitted, dicarboxylic acid coupled by glutamic acid spacer at B29
- Forms multi-hexamers with zinc core
- Some degree of albumin binding
- Half life 25 hours, glucose lowering effect for 42 hours
- Less clinical hypoglycemia than glargine
- Once daily any time of day
Another approach to reducing the number of units/day that are necessary for control.....

• T2DM with A1c between 7-10% baseline on glargine 20-50 units/day + MET
• Randomized to liraglutide/degludec 100/3.6 single daily injection or basal/ bolus insulin (glar/aspart)- 3-4 injections/day [both groups got MET]
• After 26 weeks, A1c decrease: -1.5% vs -1.5%
• Hypoglycemia 1.1% vs 8.2%; weight change -2lbs vs.+5.7lbs
• Insulin pre-trial units 34/day, end of trial 52 units basal and 32 units bolus
• Liraglutide/degludec units pre-trial 34/day, end of trial 40 units

BillingsLK et al. Diab Care 2018;41(5);1009-1016
Insulin cost- ugh

• Does it really have to be so complicated?......list price confusion
• Rebates to PBM’s- who actually benefits?
• High deductible insurance plans- basically cash pay patients for a while
• Donut hole- less an issue than previously
• Patient support programs- some are generous
• Human insulin product at Walmart $24.88 10ml
U-500 cost

• Big one time out of pocket potential
• $220 per vial in 2007, $1444 per vial in 2019
• However may be able to consolidate two insulin products into one copay
• Potential for better control in resistant patients
• Insulin glargine U-300 and insulin degludec U-200 basal may shift this market
• U-500 has about 5% of the market, estimates indicate this may expand to 17% of the market by 2025 (increasing obesity component with more insulin resistance)
• Pens reduce dosing errors
PRICE OF INSULIN: U500 vs U100

Based on average $USD wholesale prices.
Medicare Part D LIS (Low Income Subsidy) Program

• Applies to all Part D medications, not just diabetes drugs
• Applies to patients at or below federal poverty levels (eligibility not ruled out if own house, car, life insurance)
• May qualify for **Full** extra help or **Partial** extra help
• Full extra help- no monthly premium, no annual deductible, no donut hole; copay $3.70-$8.35 (brand names) and $1.25-$3.40 (generics)
• Partial extra help- sliding scale monthly premium, annual deductible $85, no donut hole, up to 15% coinsurance; copay $8.35 (brand names) and $3.40 generics
• [www.ssa.gov/medicare/prescriptionhelp](http://www.ssa.gov/medicare/prescriptionhelp) or 1-800-772-1213
• If denied, use denial letter with patient assistance application
Why diabetes care is so hard.....

• Lifestyle changes, every day
• Diabetes care is the antithesis of urgent care
• Diabetes kills the patient only a few cells at a time
• Multiple organ systems at risk- heart, vasculature, nerves, eyes, kidneys, reproductive, skin
• Provider knowledge and education on diabetes is inconsistent
• Patient education is worse in consistency
• Mediocre compensation for diabetes care, needs a team led by a quarterback than can share information
• High cost- pay now, pay later or both