Update on Management of Diabetes Mellitus - 2016

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Disclosures for Dr. Lillian F. Lien

The Department of Medicine requests the following disclosures to the lecture audience:

Disclose relevant financial relationships with any commercial interest:

<table>
<thead>
<tr>
<th>Commercial Interest</th>
<th>Role</th>
</tr>
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<tbody>
<tr>
<td>Springer</td>
<td>Book royalties</td>
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<td>Sanofi-Aventis</td>
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<td>Merck</td>
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<td>Eli Lilly</td>
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<td>Novo Nordisk</td>
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Objectives

- Brief “Sample” Case
- Glycemic Targets
- SQ Insulin and Weight-Based Dosing
- New Insulins
- New Oral agents for Type 2
- Safety
Hypothetical Case Scenario

- A 45 yo female with Type 1 DM takes 8 units of SQ glargine (Lantus) each morning. (She takes mealtime short-acting insulin as well).
- She is admitted to the hospital for volume overload in the setting of ESRD.
- Her medication record reflects the plan for her to receive 8 units glargine (Lantus) at 0800 each morning.
- One morning, the RN taking care of the patient contacts the primary team provider to state the patient missed the 0800 glargine dose due to transport to dialysis. She asks the provider what to do.

  If you are the provider receiving this call, what would you do?

- Provider chooses to write a new SQ glargine order, 8 units to be given qHS.
- At midnight, the patient has a point-of-care blood glucose test which shows a level of 350 mg/dL.

  What would you do?

- The covering night-time provider then orders SQ regular insulin 15 units to be given X 1 now.

- The patient’s BG is found to be 52 mg/dL at the 6am glucose check. Dextrose 50% IV is given immediately, with a recheck of BG approximately 20 min later showing a value of 80 mg/dL, and the patient was asymptomatic with no adverse sequelae.
The first goal of inpatient diabetes management is safety

- When called about hyperglycemia, what do you say?
  - Clarify Type of Insulin and when Last Dose given
  - What type of diabetes mellitus?

- Themes:
  - Teamwork and communication (RN/MD/NP/Pharm)
  - Trends are more important than isolated episodes

- Why does this matter?
  Safety. Satisfaction. Scope of the Epidemic…
Overview of Diabetes Mellitus in the United States

In 2003:
People With Diabetes: 17 million
(6.2% of total population)

People Without Diabetes: 257.2 million

Diagnosed: 11.1 million
Undiagnosed: 5.9 million

In 2014: CDC Statistics

Diabetes affects 29.1 million people
9.3% of the U.S. population

DIAGNOSED 21 million people
UNDIAGNOSED 8.1 million people

NIDDK. *Diabetes Statistics. 5/2003*, NIH Publication No. 02-3892
CDC. *National Diabetes Fact Sheet 2011*
Among U.S. residents aged 65 years and older, 11.2 million, or 25.9%, had diabetes per 2009-2012 NHANES and Census data.

In 2012 ... an estimated 86 million American adults, aged 20 years or older, [have] prediabetes.
Diabetes Definitions and Goals of Treatment
Diabetes Definitions

- **FPG >126 mg/dl (7.0 mmol/l):** Fasting is defined as no caloric intake for at least 8 h.
- **Two-hr plasma glucose >200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT):** using a glucose load containing the equivalent of 75 g glucose.
- **In a patient with classic symptoms of hyperglycemia, a random plasma glucose >200 mg/dL (11.1 mmol/l).**
- **A1C ≥6.5%:** The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the DCCT assay.
Types of Diabetes Mellitus

- **Type 1 diabetes (5-10%)**
  - Formerly “Type I”, “IDDM”, “Juvenile Onset”
  - Caused by destruction of insulin producing cells

- **Type 2 diabetes (90-95%)**
  - Formerly “Type II”, “NIDDM”, “Adult Onset”

- **Gestational diabetes**
  - Diabetes develops during pregnancy and resolves after pregnancy

- **LADA – Latent Autoimmune Diabetes of Adulthood**

- **MODY – Maturity Onset Diabetes of the Young**

- **Other causes (Cystic Fibrosis, Medication-Induced)**
Why Type 1 is very different from Type 2 Diabetes Mellitus...

Patients with Type 1 are not safe Without Basal Insulin
- Always give Basal Insulin (Lantus, Levemir, NPH) to your type 1 patient
- Never Hold Basal insulin UNLESS BG is <80mg/dL
  In that case, treat the patient. Once BG is above 80mg/dL, then be sure to give the Basal insulin at that point, to avoid DKA later

Patients with Type 1 are Very Insulin Sensitive so need Small Amounts!
- Many patients with Type 1 have a total basal dose < 10 units
- Correction for Type 1 should only be 1-4 units at the most – whereas Correction for Type 2 can be much more.
- Always ask “Does the pt have Type 1 or Type 2”
Glycemic Goals in the Hospital

The current American Diabetes Association recommended range for glucoses in the hospital is:

- A) 80 mg/dL – 110 mg/dL
- B) 100 mg/dL – 120 mg/dL
- C) 140 mg/dL – 180 mg/dL
- D) 100mg/dL – 200 mg/dL
- E) 150 mg/dL – 200mg/dL
Standards of Medical Care in Diabetes 2015.
Diabetes Care 2015; 38(Suppl. 1):S80–S85

“If treated with insulin, generally premeal blood glucose targets of, 140 mg/dL (7.8 mmol/L) with random blood glucose, 180 mg/dL (10.0 mmol/L) are reasonable, provided these targets can be safely achieved. More stringent targets may be appropriate in stable patients with previous tight glycemic control. Less stringent targets may be appropriate in those with severe comorbidities.”
Diabetes Mellitus and Inpatient Hospitalization: The need for optimal control

- Van den Berghe et al:
- Intensive care patients were randomized to one of two groups:
  - one group received intensive insulin therapy for glucose > 110mg/dL, with maintenance values between 80 - 110mg/dL
  - the other group underwent conventional treatment: maintenance values between 180 and 200mg/dL
- The study showed substantial reductions in intensive care unit mortality, in-hospital mortality, and morbidity
  - Intensive care unit mortality was reduced from 8.0% in the conventional group to 4.6% in the intensive group (p<0.04)

## Table 1
Summary Data of Randomized Controlled Trials of Intensive Insulin Therapy to Achieve Tight Glycemic Control

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIGAMI (33), 1995</td>
<td>620</td>
</tr>
<tr>
<td>Van den Berghe et al (5), 2001</td>
<td>1,548</td>
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<tr>
<td>DIGAMI 2 (34), 2005</td>
<td>1,253</td>
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<tr>
<td>Van den Berghe et al (16), 2006</td>
<td>1,200</td>
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<tr>
<td>HI-5 (35), 2006</td>
<td>240</td>
</tr>
<tr>
<td>GluControl (27), 2007</td>
<td>1,101</td>
</tr>
<tr>
<td>Gandhi et al (36), 2007</td>
<td>399</td>
</tr>
<tr>
<td>VISEP (13), 2008</td>
<td>537a</td>
</tr>
<tr>
<td>De La Rosa et al (28), 2008</td>
<td>504</td>
</tr>
<tr>
<td>NICE-SUGAR (14), 2009</td>
<td>6,104</td>
</tr>
</tbody>
</table>

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*ALD = admission laboratorial data; BMI = body mass index; CTN = control; CV = coronary; DM = diabetes; EBR = early biochemical recovery; GAD = glycemic achievements; GES = glycemic effect size; HbA1c = glycated hemoglobin; HLD = hospital length of stay; IQR = interquartile range; LBM = left ventricular mass; MAP = mean arterial pressure; MI = myocardial infarction; NICE = national institute of clinical excellence; NICE-SUGAR = National Institute for Health and Clinical Excellence; PCI = percutaneous coronary intervention; PP = period prevalence; RCT = randomized controlled trial; RHR = relative heart rate; SUGAR = survival, glycemic, and cardiovascular outcomes; TCD = treatment control group; TG = triglycerides; WBC = white blood cells.
"NICE-SUGAR Study on Intensive Versus Conventional Glucose Control In Critically Ill Patients" March 24, 2009 NEJM

“More than 6,100 patients (multi-center) with hyperglycemia in critical care units were randomized to intensive glucose control (insulin infusion with target blood glucose between 80-108 mg/dl) or to conventional glucose control (insulin infusion begun if blood glucose was over 180 mg/dl, and discontinued if blood glucose dropped below 144 mg/dl).”

- "Patients in the intensive glucose control group were 14 percent more likely to die compared to critically ill patients in the conventional glucose control group."

- It is important to consider that the severely ill patients in this trial were treated intensively with intravenous insulin to very tight targets (average of 115 mg/dl), and were compared to a control group whose glucose control was good (insulin infusion begun if blood glucose was over 180 mg/dl, and discontinued if blood glucose dropped below 144 mg/dl).

- The ADA and AACE caution against letting this study swing the pendulum of glucose control too far in the other direction where providers in hospitals are complacent about uncontrolled hyperglycemia.

- Joint Statement from the ADA and AACE on the NICE-SUGAR Study on Intensive Versus Conventional Glucose Control In Critically Ill Patients – March 24, 2009
Summary of glycemic recommendations
– ADA Position Statement 2014
DIABETES CARE, VOLUME 37, SUPPLEMENT 1, JANUARY 2014

**A1C <7.0%**
- Goals should be individualized based on: duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, individual patient considerations

**Diabetes Care in the Hospital**
- *Insulin therapy should be initiated...starting at a threshold of no greater than 180 mg/dL (10 mmol/L).*
- A glucose range of 140–180 mg/dl (7.8 to 10 mmol/L) is recommended for the majority of critically ill pts
- *More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L) may be appropriate for selected patients, as long as this can be achieved without significant hypoglycemia.*
- Non–critically ill patients: the premeal blood glucose targets generally <140 mg/dL (7.8 mmol/L) with random blood glucose <180 mg/dL (10.0 mmol/L)
Insulin

Source: Lien and Rodgers Insulin Pharmacology Talk 2009
# Types of Insulin

<table>
<thead>
<tr>
<th>Type</th>
<th>Product</th>
<th>Brand</th>
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<tbody>
<tr>
<td>Rapid-Acting</td>
<td>Lispro</td>
<td><em>Humalog</em></td>
</tr>
<tr>
<td></td>
<td>Aspart</td>
<td><em>Novolog</em></td>
</tr>
<tr>
<td></td>
<td>Glulisine</td>
<td><em>Apidra</em></td>
</tr>
<tr>
<td>Short-Acting</td>
<td>Regular</td>
<td>“R” <em>Humulin, Novolin, ReliOn</em></td>
</tr>
<tr>
<td>Intermediate-Acting</td>
<td>NPH</td>
<td>“N” <em>Humulin, Novolin, ReliOn</em></td>
</tr>
<tr>
<td>Basal</td>
<td>Glargine</td>
<td><em>Lantus</em></td>
</tr>
<tr>
<td></td>
<td>Detemir</td>
<td><em>Levemir</em></td>
</tr>
<tr>
<td>Premixed</td>
<td>70/30 regular</td>
<td><em>Humulin, Novolin, ReliOn</em></td>
</tr>
<tr>
<td></td>
<td>75/25 lispro</td>
<td><em>Humalog 75/25</em></td>
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<tr>
<td></td>
<td>70/30 aspart</td>
<td><em>Novolog Mix 70/30</em></td>
</tr>
<tr>
<td></td>
<td>50/50</td>
<td><em>Humulin, Humalog</em></td>
</tr>
</tbody>
</table>

*Source: Lien and Rodgers Insulin Pharmacology Talk 2009*
**Insulin Dynamics**

- **Plasma Insulin Level**
  - Lispro
  - Aspart
  - Glulisine
  - Regular
  - NPH
  - Glargine (Lantus)
  - Or
  - Detemir (Levemir)

Source: Lien and Rodgers Insulin Pharmacology Talk 2009
Diabetes Management

- Dosing Info for SQ Insulin: KEY is WEIGHT-BASED Total Daily Dose

- Type 1 – start 0.3-0.5 units/kg/day
  - Often quite sensitive; start on low end

  **EXAMPLE:** 100 kilogram patient \( \times \) 0.3 units/kg/day
  \[= 30 \text{ units/day} = \text{Total Daily Dose}\]

- Type 2 – start 0.3-0.7 units/kg/day
  - New to insulin: start on low end
  - Some patients may require > 1 unit/kg/day

  **EXAMPLE:** 100 kilogram patient \( \times \) 0.5 units/kg/day
  \[= 50 \text{ units/day} = \text{Total Daily Dose}\]

Lien LF, Cox ME, Feinglos MN, Corsino L. (eds.)
Regimen intensification – How?

- A 60 yo patient with Type 2 Diabetes Mellitus has been taking Metformin 1000mg twice daily and Glipizide 10mg twice daily. He admits he has been stressed lately and not watching his nutrition. Today, his Hgb A1c is 11.5%. Weight: 100kg. Will you choose to:
  
  - A) Continue same regimen but add Actos (pioglitazone)
  - B) Stop Metformin, Stop Glipizide, and Start Lantus 50 units daily
  - C) Stop Metformin, Stop Glipizide, and Start Lantus 25 units daily, and Start Novolog 8 units three times daily with meals
  - D) Continue Metformin, Continue Glipizide, and Start Lantus 25 units daily
  - E) Continue same regimen but add Lantus 8 units daily
Diabetes Management

- **Distribution of the Total Daily Dose**
  - Basic Starting Regimens: *(Type 2...)*
    - (Oral plus) **Basal** Insulin Therapy (1-injection)
    - **Premixed** Insulin Therapy (2-injections)
  - Intensification: *(Type 1 and Type 2)*
    - Most Intensive: **Basal-Bolus** Insulin Therapy (4-shots)
    - In between: **Stepwise Addition** of Bolus Insulin to Basal Insulin

*Leahy JL. “Insulin Therapy in Type 2 Diabetes Mellitus” Endocrinol Metab Clin North Am 01-MAR-2012; 41(1): 119-44*
Key Points: Basal Insulin Therapy

- Once daily insulin injection seldom provides adequate glucose control \textit{alone} ...
- But may be used in combination with oral hypoglycemic agents in patients with Type 2 DM
- The basal component should be estimated at approximately 50% of the Total Daily Dose
  - Should not equal 100% Total Daily Dose to avoid inappropriate coverage of prandial needs with basal insulin ...
  - risk of hypoglycemia

\textbf{EXAMPLE:} 100 kilogram patient $\times$ 0.3 units/kg/day
= 30 units/day = Total Daily Dose

\textbf{BASAL (Lantus or Levemir)* Insulin} = Give only 15 units once* daily!


* Discussion: BID analogues for type 1. BID NPH for cost.
Insulin Regimens

- **Four Injections Daily**
  - Using rapid-acting insulin (bolus) and long-acting, peakless insulin (basal)

  - One-sixth of the total daily dose is administered before breakfast, lunch, and dinner as rapid-acting insulin (Humalog or Novolog or Apidra)

  - One-half of the total daily dose is administered once daily* as a long-acting, peakless insulin (Lantus or Levemir)

EXAMPLE: 100 kilogram patient $\times$ 0.3 units/kg/day = 30 units /day = Total Daily Dose

- Basal Dose: 15 units daily
- Bolus Dose: 5 units with each meal

Insulin Regimens

**Four Injections Daily**

- **Using regular insulin and NPH insulin**
  - One-fourth of the total daily dose is administered as regular insulin before breakfast, lunch, and dinner
  - One-fourth of the total daily dose is administered as NPH insulin prior to bedtime

**EXAMPLE:** 100 kilogram patient \( \times \) 0.3 units/kg/day = 30 units /day = Total Daily Dose

(with rounding…)

8 units Regular TIDAC
8 units NPH qHS

Lien et al. “In-hospital Management of Type 2 Diabetes Mellitus”
Diabetes Management

- **Stepwise Addition of Bolus Insulin to Basal Insulin**
  - Adding prandial insulin in a stepwise fashion to patients with optimized basal insulin is still being validated.
  - One-by-one addition of mealtime insulin to optimized basal insulin is less intimidating for most patients and providers.

**EXAMPLE:** 100 kilogram patient \( \times \) 0.3 units/kg/day = 30 units /day = Total Daily Dose

- Basal Dose: 15 units daily
- Bolus Dose: 5 units at … WHICH MEALS?

Leahy JL. “Insulin Therapy in Type 2 Diabetes Mellitus” *Endocrinol Metab Clin North Am* 01-MAR-2012; 41(1): 119-44
- Insulin kinetics
  - Onset of action, peak, duration
- Insulin concentration
  - “the amount of a component in a given area or volume”
  - units / ml
The past...

- **Intravenous insulin concentration**
  - Most intravenous insulin infusions are delivered from bags with:
  - "1:1" insulin infusion = 1 unit/ml concentration

- **Subcutaneous insulin concentrations**
  - **U-100**
    - Normal SQ insulins, of which we are most familiar, all come in the concentration **U-100**, which means 100 units/ml.
  - **U-500**
    - An alternative Highly Concentrated insulin does exist: U-500 Insulin is 5x more concentrated (=500 units/ml) than the standard U-100.
Why U-500 concentrated insulin?

- Treatment of diabetic patients w/ marked insulin resistance
  - Typically type 2 DM with obesity
  - Requiring >200 units daily

- This subset of diabetic patients is expected only to continue to increase due to obesity in the U.S.
Safety Issues To Consider

- U-500 Regular Insulin is 5x more concentrated than the standard U-100 Regular insulin
- Potential for dosing errors with two types of SQ insulin concentrations available
- **Why dosing errors?**
  - All existing insulin syringes are designed only for the U-100 concentration of insulin
- **How to prevent dosing errors?**
- Use proper specially designed syringes – with markings calibrated for the different concentrations of insulin – OR
- Insulin pens where ONLY UNITS are available for patient choice – and volume is essentially hidden
U-500 – the old and new

- The old status quo:
  - No syringe, No pen
  - In many hospitals, only the Pharmacist is allowed to prepare single dose syringes of U-500 for distribution.
  - Doses will be prepared *only* in TB syringes
    - Highlights the Distinction of U-500 insulin from other insulins
    - Labeled w/ High-alert medication stickers
  - Goal – avoid “calculated conversions”

- The new: “FDA Approves First U-500 Insulin Pen Device”
  - “This FDA approval is the first in the world for the Humulin R U-500 KwikPen”, now, in 2016
New categories

- Insulin kinetics
  - Onset of action, peak, duration

- Insulin concentrations – units/ml
  - Newest concentrated insulins do have:
    - Insulin pens where ONLY UNITS are available for patient choice – and volume is essentially hidden

- Insulin formulations
  - SQ
  - Inhaled
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<th>Brand</th>
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<th>Pen</th>
<th>Unique Issues</th>
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<td>Humulin R U-500</td>
<td>Regular U-500</td>
<td>U-500</td>
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<td>Glulisine Aspart</td>
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<td>Basal</td>
<td>Yes to 80</td>
<td>Flatter profile so may less hypo Onset-Duration 8-42 hours allows &quot;any hour&quot; &quot;flex&quot;dose</td>
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<td>Ryzodeg</td>
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<td>U-100</td>
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<td>Basaglar</td>
<td>Glargine biosimilar</td>
<td>U-100</td>
<td>Basal</td>
<td>Yes</td>
<td>“follow-on” or “biosimilar”</td>
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Toujeo (insulin glargine U-300)

- Concentration U-300 (300 units/ml)
- Basal insulin
- Similar to Lantus – suggested dosing is once daily at any time during the day - “at the same time of day, every day”
- Dose – regardless of the ‘concentration’, always dose in units – preferably weight based dosing (units / kg)
  - “Higher concentration” does NOT mean you should lower the dose
  - When switching from Lantus, use the SAME DOSE
- The only caveat to 1:1 dosing – *lower bioavailability*
  - “Unit for unit, patients started on, or changed to, Toujeo® required a higher dose than patients controlled with Lantus®. When changing from another basal insulin to Toujeo®, patients experienced higher average fasting plasma glucose levels in the first few weeks of therapy until titrated to their individualized fasting plasma glucose targets. Higher doses were required in titrate-to-target studies to achieve glucose control similar to Lantus®.”
- Indicated to improve glycemic control in adults with diabetes mellitus
  - Not recommended for management of DKA
- Pen – prefilled “Toujeo 300 units/mL SoloStar”
- Onset of action: ~ 6 hours. Duration ~ 36 hours
- “no clinically important differences in hypoglycemia between Toujeo and Lantus among Type 1”

* Toujeo product information (package insert)
* [https://www.toujeopro.com](https://www.toujeopro.com)
**Tresiba – insulin degludec**

- **Concentrations:**
  - U-100 (100 units/ml) and ALSO:
  - U-200 (200 units/ml)

- **Basal Insulin – NEW long-acting human insulin analog – degludec –**
  - "forms multi-hexamers when injected... resulting in a SQ degludec depot. The protracted time action profile ... is predominantly due to a delayed absorption of insulin degludec from the SQ tissue to the systemic circulation and to a lesser extend due to binding of insulin degludec to circulating albumin"

- **Dose** – regardless of the ‘concentration’, always dose in units – preferably weight based dosing (units / kg)
  - "Do NOT perform dose conversion.... The ...dose window shows the number of insulin units to be delivered and NO conversion is needed"

- **Administration** –
  - Onset – 8 hours. “Ensure that at least 8 hours have elapsed between... injections”
  - Duration - ~42 hours = Give once daily at any time of day – and (with the above caveat,) the next daily dose can also be at any time of day – “flex dosing”

- **Flatter profile may lead to less hypoglycemia** -
  - J Clin Endocrinol Metab. 2013 Mar;98(3):1154-62. This trial showed that flex dosing of 8-40 hour range had less nocturnal hypoglycemia THAN FIXED tresiba or lantus dosing. No change in General hypoglycemia.

- **Indications** – indicated to improve glycemic control; Not recommended for managing DKA

- **Pens:**
  - Tresiba U-100 FlexTouch pen – up to 80 units in a single injection
  - Tresiba U-200 FlexTouch pen – up to 160 units in a single injection

- **Tresiba product information (package insert)**
- **https://www.tresibapro.com**
References

- Toujeo product information (package insert)
  - https://www.toujeopro.com
- Tresiba product information (package insert)
  - https://www.tresibapro.com
- Basaglar product information (package insert)
  - https://www.basaglar.com/
- Regular Insulin U-500 product information (package insert)
Major Metabolic Defects in Type 2 Diabetes

- Peripheral insulin resistance in muscle and fat
- Decreased pancreatic insulin secretion
- Increased hepatic glucose output

Haffner SM, et al. Diabetes Care, 1999
GLP-1: effects in humans

GLP-1 is secreted from L-cells of the jejunum and ileum.

That in turn...

After food ingestion...

- Stimulates glucose-dependent insulin secretion
- Suppresses glucagon secretion
- Slows gastric emptying
- Leads to a reduction of food intake
- Improves insulin sensitivity

Long-term effects in animal models:
- Increase of β-cell mass and improved β-cell function


Courtesy: National Lipid Association
<table>
<thead>
<tr>
<th>Non-Insulin Anti-Diabetic Medication</th>
<th>•Class</th>
<th>Approved Pre-2005</th>
<th>Approved Post-2005</th>
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<tbody>
<tr>
<td>Glipizide (Glucotrol), Glimepiride (Amaryl), Glyburide (Diaβeta, Glynase PresTabs, Micronase)</td>
<td><strong>Sulfonylurea</strong></td>
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<td></td>
</tr>
<tr>
<td>Metformin (Glucophage, Glucophage XR)</td>
<td><strong>Biguanide</strong></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Pioglitazone (Actos), Rosiglitazone (Avandia)</td>
<td><strong>Thiazolidinedione</strong></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Repaglinide (Prandin), Nateglinide (Starlix)</td>
<td><strong>Meglitinide</strong></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Acarbose (Precose), Miglitol (Glyset)</td>
<td><strong>Alpha-glucosidase inhibitor</strong></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Tradjenta)</td>
<td><strong>DPP-IV inhibitor</strong></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Exenatide (Byetta), Liraglutide (Victoza) (Tanzeum, Trulicity, Bydureon)</td>
<td><strong>GLP-1 mimetic</strong></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Pramlintide (Symlin)</td>
<td><strong>Amylin mimetic</strong></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Bromocriptine mesylate (Cycloset)</td>
<td><strong>Dopamine receptor agonist</strong></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Canagliflozin (Invokana)</td>
<td><strong>SGLT2 inhibitor</strong></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Dapagliflozin (Farxiga)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empagliflozin (Jardiance)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- Blocks reabsorption of glucose; increases its excretion in urine
- Infection? Euglycemic DKA?
A 60 yo patient with Type 2 Diabetes Mellitus has been taking Metformin 1000mg twice daily. He admits he has been stressed lately and not watching his nutrition. Today, his Hgb A1c is 9.5%. Weight: 100kg. Will you choose to:

- A) Continue Metformin but Add Glipizide
- B) Continue Metformin but Add Januvia
- C) Continue Metformin but add Lantus
- D) Continue Metformin but add a GLP1-agonist (Byetta, Bydureon, Victoza, Tanzeum, or Trulicity)
# Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

**Position Statement**

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

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### Initial drug monotherapy

<table>
<thead>
<tr>
<th>Efficacy (HbA1c)</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>high</td>
<td>low</td>
<td>neutral</td>
<td>high</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>low</td>
<td>moderate</td>
<td>rare</td>
<td>low</td>
</tr>
</tbody>
</table>

If needed to reach individualized HbA1c target after ~3 months, proceed to two-drug combination (order not meant to denote any specific preference):

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

- **Sulfonylurea**
  - high
  - moderate risk
  - gain
  - hypoglycemia
  - low

- **Thiazolidinedione**
  - high
  - low risk
  - gain
  - edema, HF, Fxs
  - high

- **DPP-4 Inhibitor**
  - intermediate
  - low risk
  - neutral
  - rare
  - high

- **GLP-1 receptor agonist**
  - high
  - low risk
  - loss
  - Gf
  - high

If needed to reach individualized HbA1c target after ~3 months, proceed to three-drug combination (order not meant to denote any specific preference):

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

- **Insulin (usually basal)**
  - highest
  - high risk
  - gain
  - hypoglycemia
  - variable

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2015 UPDATED article: Diabetes Care 2015;38:140–149
Metformin previously had been contraindicated for patients with renal disease or dysfunction, as suggested by serum creatinine levels at or above 1.5 mg/dL for men and 1.4 mg/dL for women or abnormal creatinine clearance.

The FDA now says that after reviewing a number of studies, it has concluded that this contraindication is no longer necessary for certain patients with reduced kidney function. The reason for the contraindication was that patients with reduced renal function are at higher risk of developing lactic acidosis, a very rare side effect associated use of metformin.

• Before starting metformin, obtain the patient’s eGFR.
• Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m².
• Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m² is not recommended.
• Obtain an eGFR at least annually in all patients taking metformin. In patients at increased risk for the development of renal impairment such as the elderly, renal function should be assessed more frequently.
• In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m², assess the benefits and risks of continuing treatment. Discontinue metformin if the patient’s eGFR later falls below 30 mL/minute/1.73 m².

Quotes above from news source: Medscape Medical News, April 8, 2016
Insulin Administration Issues
Diabetes Management Safety
Factors that affect SQ insulin absorption:

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Strenuous use of injected limb within one hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massage of area</td>
<td>Do not rub site vigorously</td>
</tr>
<tr>
<td>Temperature</td>
<td>Heat increases, cold decreases</td>
</tr>
<tr>
<td>Site of Injection</td>
<td>Abdomen&gt;arms&gt;thigh (R &amp; N only)</td>
</tr>
<tr>
<td>Lipohypertrophy</td>
<td>Delays absorption</td>
</tr>
<tr>
<td>Large doses (&gt;80 units)</td>
<td>Delay onset and duration</td>
</tr>
</tbody>
</table>

Adapted from www.endotext.org, 2004

Factors in the hospitalized patient

- Severity of illness
- Medications: glucocorticoids, pressors
- Diet: different, tube feeds, unpredictable
  - Caution: coordination of timing of insulin administration and meals or NPO status

Insulin Safety

- Key clinical data:
  - Type of Diabetes
  - Weight accounted for in dosing
  - Renal Function
  - Steroids
  - Nutrition
  - History of hypoglycemia

- Encourages use of current best practices
  - Basal/bolus scheduled insulin
  - Move away from “SSI”
  - Safe ‘correction dose’ scales
Diabetes Management

- Blood glucose monitoring
  - qac, qhs, and q3am if eating
  - q6hrs if NPO
- Correction dose insulin
  - use 5% rule
  - to be given qac only... NOT at hs or 3am!
- Nutrition consult
- Educate patient regarding management of lows
- If persistent high BGs suspect DKA—check labs accordingly!
- Do Not Stack Insulin
• **“Insulin Stacking”**
  
  – Repeating SQ insulin dose before prior dose wears off.

• **How to avoid this?**
  
  – Next dose no sooner than 3 hours after last dose of SQ rapid-acting (log) insulin
  
  – Wait at least 4 hours between SQ regular insulin doses

Source: Lien and Rodgers Insulin Pharmacology Talk 2005
**Pathways to Quality Inpatient Management of Hyperglycemia and Diabetes: A Call to Action**


*Lien L is an author in the writing group: Planning Research in Inpatient Diabetes

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**System-level interventions**
- Hospital-wide hyperglycemia and hyperglycemia policies and order sets through central glucose management programs
- Education tools to improve provider knowledge (nursing, physicians, mid-level care providers, pharmacists)
- Clinical decision aids at point of care

**Patient-level interventions—treatment**
- Insulin and/or incretin-based therapies for special patient populations—enteral and parenteral nutrition, glucocorticoids, organ transplantation, dialysis, labor & delivery, insulin pump

**Patient-level interventions—discharge planning**
- Appropriate discharge to home processes

**Improved Processes of Care**
- Initiating appropriate components of insulin therapy (scheduled instead of sliding scale insulin use)
- Appropriate daily adjustments to insulin
- Appropriate nutritional insulin administration practices
- Protocol-driven response to hypoglycemia
- Protocol adherence

**Improved Intermediary Glucose Outcomes**
- % of readings within hypoglycemic, euglycemic, or hyperglycemic range.
- % of patient hospital days with an episode of hypoglycemia (e.g., <40 mg/dL) or hyperglycemia.
- % of patient hospital days with day-weighted mean BG in euglycemic & hyperglycemic range
- Overall mean patient-day or patient-stay blood glucose

**Improved clinical and Economic Outcomes**
- Decreased LOS
- Decreased cost of admission
- Decreased incidence of readmission for hyperglycemia, or DKA
- Decreased rates of inpatient mortality, nosocomial infections

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**Figure 1**—Diagram of a conceptual model for pathways to quality inpatient management of hyperglycemia and diabetes, adapted from Munoz et al. (18).
Final Thoughts

• In-hospital management of the patient with diabetes poses many challenges but also a unique opportunity to improve glycemic control and patient care. Should be considered a window of opportunity.

• Proper administration of subcutaneous and intravenous insulin, as well as appropriate use or discontinuation of oral hypoglycemic agents, can reduce the complexity of a patient’s hospital course and potentially reduce overall morbidity and mortality.
Extra Slides
For women with pre-existing type 1 or type 2 diabetes who become pregnant, the following are recommended as optimal glycemic goals, if they can be achieved without excessive hypoglycemia (104):

- Premeal, bedtime, and overnight glucose 60–99 mg/dL (3.3–5.4 mmol/L)
- Peak postprandial glucose 100–129 mg/dL (5.4–7.1 mmol/L)
- A1C <6.0%

ADA Standards, DIABETES CARE, VOLUME 37, SUPPLEMENT 1, JANUARY 2014
RABBIT2 and RABBIT2 Surgery


  - Treatment with insulin *glargine and glulisine resulted in significant improvement in glycemic control compared with that achieved with the use of SSI alone.*
    - 130 pts DM2 (multi-center) RCT to receive *glargine and glulisine* (*n=65*) or a standard SSI protocol (*n 65*).
    - Despite increasing insulin doses, 14% of patients treated with SSI remained with blood glucose 240 mg/dl. There were no differences in the rate of hypoglycemia.

  - There were *reductions with basal-bolus* as compared with SSI [24.3 and 8.6%; odds ratio 3.39 (95% CI 1.50–7.65); *P = 0.003*] in the composite outcome of wound infection, pneumonia, bacteremia, and respiratory and ARF.
Humalog

- EMR needs to account for two different concentrations:
  - Humalog U-100
  - Humalog U-200
Basaglar (insulin glargine)

- Concentration: U-100 (100 units/ml)
- US FDA regulatory term: “follow-on biologic to Lantus”
  - “Two phase 3 studies, one for type 1 diabetes and one for type 2 diabetes, were conducted to determine BASAGLAR noninferiority to US- or non-US-approved Lantus as measured by change in A1C from baseline”
- Around the world: “biosimilar to glargine”
  - “with an identical amino acid sequence to that of Lantus® (insulin glargine injection)”
- Basal insulin
- Similar to Lantus – suggested dosing is once daily “at the same time of day, every day”
  - “sustained glucose lowering activity over 24 hours with no pronounced peak”
- Indicated to improve glycemic control in patients with Type 1 and Type 2
- As with Lantus, not recommended for management of DKA
- Pen: prefilled “BASAGLAR KwikPen”

- Basaglar product information (package insert)
- https://www.basaglar.com/#