Evolving insulin therapy: Insulin replacement methods and the impact on cardiometabolic risk

Harvard/Joslin Primary Care Congress for Cardiometabolic Health 2013

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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
### Aggressive Control of Diabetes: Glycemic Goals of Treatment

<table>
<thead>
<tr>
<th>AMERICAN DIABETES ASSOCIATION (ADA)</th>
<th>GOAL</th>
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</thead>
<tbody>
<tr>
<td>A1C (%)</td>
<td>&lt; 7</td>
</tr>
<tr>
<td>Preprandial plasma glucose (mg/dL)</td>
<td>70–130</td>
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<tr>
<td>Peak postprandial plasma glucose (mg/dL)</td>
<td>&lt; 180</td>
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</table>

<table>
<thead>
<tr>
<th>AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS (AACE)</th>
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<tbody>
<tr>
<td>A1C (%)</td>
</tr>
<tr>
<td>Preprandial plasma glucose (mg/dL)</td>
</tr>
<tr>
<td>2-hour postprandial glucose</td>
</tr>
</tbody>
</table>

A1C is “gold standard” measure of diabetes control over the previous 2–3 months

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Handelsman Y et al. AACE Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan. *Endo Prac* 17 (Suppl 2) Mar/Apr 2011.
Value of Insulin Therapy in Type 2 DM

- Overcoming glucose toxicity
- Using insulin treatment early in the natural history to optimize and/or replace first-phase insulin release
- To control fasting glucose and thus improve day-long glycemic control
- Need for insulin therapy later in the natural history to replicate both basal and prandial insulin patterns
- Individualize goals to maintain safety
Natural History of Type 2 Diabetes

**IGT**=impaired glucose tolerance  **IFG**=Impaired Fasting Glucose

Adapted from International Diabetes Center (Minneapolis, Minn).

Plasma Glucose

120 (mg/dL)

Relative β-Cell Function

100 (%)

Years of Diabetes

*IGT=impaired glucose tolerance  **IFG=Impaired Fasting Glucose
DECODE Trial: Relative Risk of Death, Shown by Blood Glucose Level

*Death due to all causes, adjusted for age, sex, study center.
Relative Contribution of FPG and PPG to Overall Hyperglycemia Depending on A1C Quintiles

Clinical Inertia: “Failure to advance therapy when required”

Percentage of Subjects Advancing when A1C > 8%

At insulin initiation, the average patient had:
- 5 years with A1C > 8%
- 10 years with A1C > 7%

ACCORD & Advance

- ACCORD: More unexpected deaths in the intensive glycemic treatment group, unrelated hypoglycemia, specific drugs Rx.
- Advance: Intensive glucose control significantly reduces risk of DM vascular complications. VADT: similar findings
- Implications: No change in guidelines. (Early aggressive control likely still a benefit)
- However, individualize treatment goals, and avoid “tight” control where it might be dangerous (CAD, elderly)

Early Insulin Treatment in Type 2 Diabetes: PROS

- Effective control with minimal weight gain and hypoglycemia
- Rapidly overcomes glucose toxicity to establish glycemic control
- Could be transitioned back to antidiabetes medication therapy if possible
- Advancement of therapy to maintain euglycemia would parallel decline in β-cell function

Meneghini LF. *Diabetes Care.* 2009;32:S266-S269.
Early Insulin Treatment in Type 2 Diabetes: CONS

- Data do not support the hypothesis that early insulin treatment reduces cardiovascular risk
- Associated with adverse effects, such as hypoglycemia, weight gain, and possibly increased cancer risk
- Nevertheless, treat to target, and insulin may be needed to do so

Comparison of Newly Diagnosed Subjects Treated with CSII, MDI, or Antidiabetes Medication for 2 Weeks after Achievement of Normoglycemia

- Comparison of CSII, MDI, or oral treatment (SU +/- or Met)
- Treatments used to rapidly establish glycemic control (F: 110, 2-h pp 144 mg/dL) within 8 days; greater percentage in the insulin groups achieved targeted control
- Treatment withdrawn after 8 days of normoglycemia, then HOMA measure of first-phase insulin release at that time and at 1 year
- By 1 year, remission rates higher in insulin groups
- Better retention of first-phase insulin release in insulin-treated groups

### Comparison of Newly Diagnosed Subjects Treated with CSII, MDI, or Antidiabetes Medication for 2 Weeks after Achievement of Normoglycemia

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<th>MDI</th>
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<td>118</td>
<td>101</td>
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<tr>
<td><strong>Age (yrs)</strong></td>
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<td>51</td>
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<tr>
<td><strong>BMI (kg/m²)</strong></td>
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<td>24</td>
<td>25</td>
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<tr>
<td><strong>Baseline A1C (%)</strong></td>
<td>9.8</td>
<td>9.7</td>
<td>9.5</td>
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<tr>
<td><strong>% Achieving euglycemia</strong></td>
<td>97</td>
<td>95</td>
<td>83</td>
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<tr>
<td><strong>Time to euglycemia (days)</strong></td>
<td>4</td>
<td>5.6</td>
<td>9.3</td>
</tr>
<tr>
<td><strong>Daily drug dose</strong></td>
<td>0.68 units/kg (mean)</td>
<td>0.74 units/kg (mean)</td>
<td>Glicazide 160 mg + metformin 1,500 mg</td>
</tr>
<tr>
<td><strong>Δ in AIR</strong></td>
<td>951</td>
<td>800</td>
<td>831†</td>
</tr>
<tr>
<td><strong>AIR (median) in remission groups at 1 year</strong></td>
<td>809</td>
<td>729</td>
<td>335†</td>
</tr>
</tbody>
</table>

*AIR = Acute insulin response (pmol • 1⁻² • min⁻¹)

†P<0.05 compared with CSII

Incremental or Decremental Values for Fasting Insulin vs Baseline at Year 1 and 2

Insulin stopped for 72 h at 1 and 2 years for testing at 48 and 72 h

†P = 0.02 Glibenclamide (glyburide) vs insulin

Diabetes Dx:
• Within 2 mos
• Age 21–70 yrs

Rx: 70/30 Premix Insulin BID + Metformin

3 months

Metformin, Glyburide, + Pioglitazone

3 years

Continue Insulin + Metformin

Comparisons of Insulin-Based vs Triple Oral Therapy: A1C, Weight, Compliance – 36 Months

A1C

Weight

Compliance

Comparisons of Insulin-Based vs Triple Oral Therapy: Hypoglycemia – 36 Months

- **Mild hypoglycemic events ($P=0.18$)**
  - Insulin group: 0.51 events / person-month
  - Triple oral group: 0.68 events / person-month

- **Severe hypoglycemic events ($P=0.53$)**
  - Insulin group: 0.04 events / person-year
  - Triple oral group: 0.09 events / person-year

Comparisons of Insulin-Based vs Triple Oral Therapy: Compliance, QOL – 36 months

- **Compliance**
  - Insulin group: 93%
  - Triple oral group: 90%

- **Quality of life**
  - No between-group differences for any of the 12 QOL domains evaluated
  - Both groups showed improvements with respect to social worries
  - All other domains remained unchanged

- Subjects randomized to the insulin group reported satisfaction with that treatment and willingness to continue at the 18-month period
ORIGIN Trial:

- A six-year randomized clinical trial to assess impact of insulin glargine Rx versus standard care on CV outcomes.
- Over 12,500 participants worldwide with pre-diabetes or early type 2 diabetes mellitus and high CV risk
- 6,264 participants randomized to receive insulin glargine titrated to achieve fasting normoglycemia.
- The co-primary endpoints were the composite of CV death, or non-fatal MI, or nonfatal stroke; and the composite of CV death, or non-fatal MI, or non-fatal stroke, or revascularization procedure, or hospitalization for heart failure.
ORIGIN Trial: Key Findings

The study demonstrated:

- Achieving fasting normoglycemia did not affect CV outcomes in subjects with early dysglycemia
  - First co-primary endpoint: $p = 0.63$, NS
  - Second co-primary endpoint: $p = 0.27$, NS

- Glargine achieved targeted long-term glycemic control (median FPG = 5.2 mmol/L and A1C 6.2%), over 6.2 years

- No association between glargine use and increased risk of any cancer ($p = 0.97$, NS).
  - All cancers combined
  - Any organ-specific type of cancer
Demonstrated a reduction in the progression to diabetes for people without diabetes at baseline (based on OGTT off insulin):

- Glargine delayed progression from pre-diabetes (IFG or IGT) to confirmed type 2 diabetes mellitus by 28% (p = 0.006).
- Reduction was 31% for confirmed plus uncertain diagnosis group
- Reduction in progression occurred despite weight gain (diabetes risk factor)
- Actual effect on β-cell function is uncertain
ORIGIN Trial: Adverse Events

- **Hypoglycemia:**
  - Severe, events per 100 patient-yr ($p<0.001$):
    - Glargine: 1 episode
    - Standard care: 0.31 episode
  - Overall hypoglycemia, events per 100 person-yr ($p<0.001$):
    - Glargine: 16.7
    - Standard Care: 5.16

- **Weight:**
  - Glargine: Increased by a median of 1.6 kg
  - Standard Care: Fell by 0.5 kg
ORIGIN Trial: Key Messages

- No increased or decreased risk of CVD with early use of glargine (basal) insulin
- No increased risk of cancer with use of glargine
- Insulin can slightly increase the risk of hypoglycemia and weight gain
- Early use of insulin *may* have a beneficial impact on short-term loss of β-cell function. Long term impact is unknown; further study is needed
**HEART2D:**

![Graph showing fraction of patients not experiencing a combined primary outcome](image)

<table>
<thead>
<tr>
<th>Days</th>
<th>Basal (n=558)</th>
<th>Prandial (n=557)</th>
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<td>1.0</td>
<td>1.0</td>
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<tr>
<td>200</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>400</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>600</td>
<td>0.7</td>
<td>0.7</td>
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<tr>
<td>800</td>
<td>0.6</td>
<td>0.6</td>
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<tr>
<td>1,000</td>
<td>0.5</td>
<td>0.5</td>
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<tr>
<td>1,200</td>
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<td>1,400</td>
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<tr>
<td>1,600</td>
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</table>

<table>
<thead>
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<th>Days</th>
<th>Prandial</th>
<th>Basal</th>
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<td>800</td>
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<td>386</td>
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<tr>
<td>1,000</td>
<td>388</td>
<td>382</td>
</tr>
<tr>
<td>1,200</td>
<td>384</td>
<td>377</td>
</tr>
</tbody>
</table>

HEART2D:

Percentage of HEART2D patients aged >65.7 years not experiencing a first CV event (CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for acute coronary syndrome) vs. days in the trial by insulin strategy.

Raz I et al. Diabetes Care 2011;34:1511-1513
Meal-induced increases in Inflammatory Markers are attenuated by prandial + basal insulin in patients with Type 2 diabetes.

Black Bars with dotted line trend:
Insulin lispro mix + Metformin

White Bars with solid line trend:
Insulin glargine + Metformin
Meal-induced increases in Inflammatory Markers are attenuated by prandial + basal insulin in patients with Type 2 diabetes.

Black Bars with dotted line trend:
Insulin lispro mix + Metformin

White Bars with solid line trend:
Insulin glargine + Metformin
Exenatide Plus Glargine: Change in Glucose Levels Over 30 weeks


*p< 0.001 for between-group dif.
†p< 0.010 for between-group dif.
Exenatide Pus Glargine: Change in Weight Over 30 Weeks

Liraglutide Plus Metformin, With and Without Detemir: Self-monitoring Glucose Profiles

Insulin is highly effective but can be perceived as being a challenge for both patients and physicians.

Basal-bolus insulin regimens require more injections but provide better insulin coverage and better glycemic control.

Insulin regimens and insulin dosing must be adjusted for each individual patient.
Key Messages: Monitoring

- The use of glycemic monitoring patterns is key to making insulin dose adjustments.
- Monitoring schedules should be individualized for each patient to gather the specific information you need to manage that person’s treatment program.
Glucose Monitoring for Regimen Adjustment

- Patients must know what they will do with the results: Action, call, other!!
- Glucose checking ≠ glucose monitoring
- Record-keeping is crucial:
  - Date/time
  - Glucose values
  - Insulin dose
  - Food and/or carbohydrate intake
  - Activity and other factors impacting glycemic patterns
Physiologic Insulin Secretion

Daytime Meals

Breakfast  Lunch  Supper  Snack

Insulin
Key Parameters Reflecting Glycemic Control

- A1C
- Preprandial glucose levels
- Postprandial glucose levels
Action Profiles of Injectable Insulins

- Regular: 6–8 Hours
- NPH: 12–20 Hours
- Basal Insulin: Glargine, Detemir

Action Profiles:
- Aspart, Glulisine, Lispro: 4–6 Hours
- Regular: 6–8 Hours
- NPH: 12–20 Hours
- Basal Insulin: Glargine, Detemir
Possible Evolution Pathways of an Insulin Treatment Program for Type 1 DM

Diagnosis of type 1 diabetes

Full-day “conventional” coverage
- BID premixed insulin
- Custom-designed “split-mix” variant

Full physiologic insulin coverage
- Bedtime long-acting analog plus
- Premeal rapid-acting insulin
Possible Evolution Pathways of an Insulin Treatment Program for Type 2 DM

- **PM insulin treatment for basal coverage**

- **Full-day “conventional” coverage**
  - BID premixed insulin
  - Custom-designed “split-mix” variant

- **Full physiologic insulin coverage**
  - Bedtime long-acting analog plus
  - Premeal rapid-acting insulin
Basal Insulin in Type 2 DM

- May continue antidiabetes medications at same dose, particularly those that reduce insulin resistance

- Add single evening insulin dose (10 U or 0.1 U/kg) at bedtime

- Adjust dose according to fasting glucose and monitor glycemic patterns throughout the day, particularly with basal insulin use
Basal Insulin in Type 2 DM (cont.)

- Adjust basal insulin based on premeal values, but watch potential for hypoglycemia at key times during the day/night

- Postmeal elevations (BG >160 mg/dL) suggest the need for premeal coverage. Options:
  - Change to a premixed or fix-mixture insulin program
  - Add premeal rapid-acting insulin to basal insulin program

- Consider stopping secretagogues with use of premeal insulin
“Split-Mix” / Premixed Insulin Therapy

**Advantages**
- Relatively easy to use
- Covers insulin requirements through most of day

**Disadvantages**
- Not an accurate replication of physiological patterns
- Greater likelihood of nocturnal hypoglycemia from peak of presupper NPH*
- Greater chance of fasting hyperglycemia as presupper NPH wears off*

*Possible solution for these problems is to split the second dose, giving rapid-acting insulin at suppertime and NPH at bedtime using custom-mixed insulins.
Considerations for Premixed Insulin Analogs

- Provide rapid- and intermediate-acting insulin in one injection without the need to mix insulins
- Can be used in a pen device for ease of use
- Ability to improve physiologic coverage pattern from a starting regimen of 1 injection of premixed insulin to 2 or 3 injections with same insulin
- Require a relatively consistent meal and exercise pattern because the ratio of rapid to intermediate insulin is fixed
- Realistic A1C goal of ≤8%
Insulin Therapy: Indications for “Basal-Bolus” Treatment

- Significant insulinopenia
- Instability of glucose patterns (usually the result of significant insulinopenia)
- Difficulty with hypoglycemia
- Lifestyle needs
- Achieving therapeutic goals
- Weight loss
Multiple Injection Program: Premeal Rapid-Acting Insulin and Basal Insulin

- Rapid-Acting Insulin
- Peakless/Basal Insulin

Meals: B (Breakfast), L (Lunch), S (Snack), HS (Dinner), B (Breakfast)
Sample Insulin Adjustment Algorithm: Premeal Rapid-Acting and Bedtime Basal Insulin

<table>
<thead>
<tr>
<th>BLOOD GLUCOSE</th>
<th>BREAKFAST</th>
<th>LUNCH</th>
<th>SUPPER</th>
<th>BED</th>
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<tbody>
<tr>
<td>0 – 70*</td>
<td>—</td>
<td>—</td>
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<tr>
<td>71 – 100</td>
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<tr>
<td>0 – 70*</td>
<td>—</td>
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</tbody>
</table>

*Basal Insulin*

*Treat with food first, retest, then use algorithmic dose.*
Carbohydrate Counting

- Carbohydrate is the food component that most affects blood glucose
- This system tracks the grams of carbohydrate consumed for the purpose of adjusting insulin doses
- The more carbohydrate consumed, the more insulin taken
- Particularly useful for people treated with variable premeal doses of rapid-acting insulin
- Requires pre- and postprandial glucose checks
Factors Influencing Therapeutic Choices

- Medical needs and treatment goals
  - A1C level and distance from target
  - Postprandial glycemia

- Safety

- Need for flexibility in treatment program

- Patient issues with respect to insulin use
  - Intellect and judgment
  - Psychosocial and cultural considerations
  - Physical capabilities and limitations
  - Other medical conditions and issues relating to use of other noninsulin medications
External Insulin Pump Using Rapid-Acting Insulin

Insulin Bolus Doses

Insulin Basal

Alternate Basals

B L S Snack HS B

Meals

Insulin Effect
Continuous Glucose Monitoring Provides a More Comprehensive Picture of the Patterns

Fingerstick Blood Glucoses (type 1)

- Glucose measurement
- Insulin bolus

Target Range

Fingerstick Blood Glucose Data

- Time: 12:00 am, 6:00 am, 12:00, 6:00 pm, 12:00 am
- Glucose levels: 400, 300, 200, 100, 0
Suggested Sequence for Assessment of Glycemic Patterns

- Fasting value
- General premeal and bedtime values and trends throughout the day
- Postprandial values – absolute levels
- Relative change, pre- to postprandial glycemic levels

Also, continually monitor nocturnal glycemia
Antidiabetes Medications → “Split Mix”
Insulin Regimen 4 Months Ago; A1C Now 6.9%; Good Control?:

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>Post-breakfast</th>
<th>Pre-lunch</th>
<th>Post-lunch</th>
<th>Pre-supper</th>
<th>Post-supper</th>
<th>Bedtime</th>
<th>2–3 AM</th>
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</table>
A Stepwise Perspective on Insulin Treatment

- Ability to identify people for whom insulin is indicated and discuss this need with them
- Capability or identified referral resources to oversee insulin treatment initiation and support
- Ability to teach insulin use:
  - Techniques
  - Knowledge and Skills for self-management
  - Spectrum of programs, from basal to pumps
- Ability to identify people for whom the current program is inadequate and advancement of therapy is indicated
- Troubleshooting
- Referral management
Take-Away Messages

- Insulin is highly effective but can pose a challenge for both patients and physicians.
- Basal-bolus regimens require more injections but provide better insulin coverage and glycemic control.
- Regimens and dosing must be adjusted for each patient.
- Monitoring of glycemic patterns is a key tool to guide therapeutic decisions.

For more information and education, log on to the Joslin Professional Education Continuum (JPEC) website: www.jpec.joslin.org