Effective Use of Prandial Insulin:
Do we need new insulins or a better approach?

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Case 1

- A 59 year old male with a 10 year history of type 2 diabetes presents for follow-up.
  - Glucose logs show FBG in 80-130s, BG in evenings often in 200s.
  - metformin 1 gm BID and glargine 36 unit QHS
  - Patient reports good adherence and is able to afford medications
  - His mealtimes are often unpredictable due to a demanding schedule. Supper is his largest meal
  - HbA1c 8.3%
Case 1

What would you do next?
- a) Start rapid acting insulin with all 3 meals
- b) Switch to premix insulin
- c) Add regular insulin sliding scale
- d) Start rapid acting insulin before the largest meal

Questions

- Should we start with 1 meal or 3 meals?
- What about carbohydrate counting?
- Do rapid acting insulin analogues provide an advantage?
- New approaches in development
Prevalence of HbA1c <7%
NHANES Data


Natural History of T2DM

• Loss of beta cell function begins before diagnosis and progresses
• Insulin resistance does not change over time

Adapted from International Diabetes Center (IDC), Minneapolis, Minnesota.
Treatment Strategy

Diagnosis

- Medication (Metformin)
- Lifestyle changes

Progressive Beta Cell Failure

- Combination Therapy
- Basal Insulin
- Basal bolus insulin

A1c <7%: 40% 63.5%


Postprandial BG Contributes more to A1c than fasting BG in moderately controlled patients

Hypoglycemia with intensive insulin therapy?

Tendency for more hypoglycemia with tighter glycemic control and more complex regimens


Start with 3 meals or 1 meal?

- 476 patients with T2DM sub-optimally controlled on basal insulin
  - Group 1: QAC glulisine
  - Group 2: Stepwise (month 0, 4, 8) glulisine starting at meal with largest BG excursion + MTF
  - Group 3: Stepwise +SFU
- 94%, 23%, and 20% received 3 injections/day in group 1,2,3 at study end

**HbA1c**

- the adjusted A1c difference failed to show noninferiority (0.228, 95% CI: −0.018–0.473)
- In patients with baseline HbA1c ≤ 8%, difference in group did show non-inferiority (0.087, 95% CI: −0.175–0.349)

![Graph showing HbA1c levels across groups](image)

**Fig. S3** Weight changes in the safety population during the randomization period. a: Glargine + three bolus injections of glulisine; b: glargine + one bolus injection of glulisine, with two further doses at months 4 and 8 if HbA1c > 7% [target PPBG 110...]

- Similar treatment satisfaction
- Greater nocturnal hypoglycemia in group 3 vs. group 2
Which Meal to Target?

- 296 T2DM uncontrolled on optimal basal insulin
- Randomized to insulin added to largest meal or meal with the largest excursion followed by 2\textsuperscript{nd}, 3\textsuperscript{rd} meal at 12, 24 weeks
- Similar A1c reduction ~1.2%
- 75\% were using 3 injections/day by study end

Meneghini et al. Endocr Pract 2011;17:727-36

What about carbohydrate counting?

- 273 patients with T2DM on 2 injections insulin/day
- Randomized to ICR or simple meal dosing (total daily meal dose split as 50\%, 33\% and 17\% for largest, middle, and smallest meal)
- Similar HbA1c reduction
- Hypoglycemia:
  - Severe hypoglycemia similar
  - Symptomatic hypoglycemia favored fixed meal dose
- Weight gain favored carb counting
- Insulin requirement higher in simple group

Bergenstal R M et al. Dia Care 2008;31:1305-1310
What about Carb Counting in T1DM?

- 169 adults T1DM A1c 7.5-12
- Immediate vs. delayed (6 month) carb counting 5-day outpatient course

<table>
<thead>
<tr>
<th>Group</th>
<th>Glycated haemoglobin (HbA1c, %)</th>
<th>Proportion of participants experiencing severe hypoglycaemia in previous six months* (N= (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate DAFNE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>9.4 (1.1)</td>
<td>14/17 (82)</td>
</tr>
<tr>
<td>Six months</td>
<td>9.4 (1.2)</td>
<td>12/67 (18)</td>
</tr>
<tr>
<td>Delayed DAFNE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>9.3 (1.1)</td>
<td>8/72 (11)</td>
</tr>
<tr>
<td>Six months</td>
<td>9.4 (1.3)</td>
<td>11/72 (15)</td>
</tr>
</tbody>
</table>

Difference between groups at six months

Mean (95% CI) 1.0 (0.5 to 1.4) –

Statistical values t=4.4, P<0.0001  \( \chi^2=0.77, P=0.68 \)

DAFNE study group;BMJ 2002;325:746
What about Carb Counting in T1DM?

- Similar frequency of hypoglycemia
- Lipids and weight similar
- CIR had better
  - Total well-being (p<0.01)
  - ADDQoL
    - Impact of DM on freedom to eat as I wish (p<0.0001)
    - Impact of DM on QOL (p<0.01)
  - DTSQ
    - Total satisfaction (p<0.0001)
    - Perceived frequency of hyperglycemia (p<0.0001)

DAFNE study group; BMJ 2002;325:746

What about the Hospital?

- Fixed carbohydrate content meals are advised in the hospital but this does not guarantee intake\(^1,2\)
- Flexible meal plans are becoming more popular as a means of improving overall patient satisfaction in hospitals.\(^3\)

1. Moghissi ES, et al. AACE and ADA. Diabetes Care 2009
Protocol

- RCT: open label, Fixed (provided if pt ate >50% of meal) vs. Flexible meal dosing
- Detemir/Aspart
- 72 hour intervention
  - Daily adjustments 10-20% of TDD
### Mean Nonfasting Glucose (mg/dl)

<table>
<thead>
<tr>
<th>Day</th>
<th>Fixed Dose</th>
<th>Flexible Dose</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>178 (47)</td>
<td>157 (49)</td>
<td>0.03</td>
</tr>
<tr>
<td>Day 2</td>
<td>185 (52)</td>
<td>175 (47)</td>
<td>0.37</td>
</tr>
<tr>
<td>Day 3</td>
<td>191 (51)</td>
<td>196 (65)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

### Postprandial Glucose (mg/dl)

<table>
<thead>
<tr>
<th>Day</th>
<th>Fixed Dose</th>
<th>Flexible Dose</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>182 (58)</td>
<td>160 (67)</td>
<td>0.06</td>
</tr>
<tr>
<td>Day 2</td>
<td>185 (47)</td>
<td>175 (47)</td>
<td>0.75</td>
</tr>
<tr>
<td>Day 3</td>
<td>203 (74)</td>
<td>175 (50)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

### Hypoglycemia

- **Proportion of patients**

  - Day 1: 59\%
  - Day 2: 19\%
  - Day 3: 15\%

  - **P-values**:
    - Fixed: P=0.08
    - Flexible: P=>0.99
Figure 1: Mean glucose stratified by median carbohydrate intake per meal
Insulin Analogues

- Targeted stabilization (basal) or destabilization (prandial) of the insulin hexamers through Zn\(^{2+}\) binding provide more physiologic dosing.


Rapid acting insulin analogues (RAIA) vs. Human Insulin

Rapid acting insulin analogs mimic physiologic prandial insulin secretion

Clinical Outcomes with Rapid Acting Insulin Analogues
Cochrane Meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>#Trials</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1DM</td>
<td>22</td>
<td></td>
<td>100.0 %</td>
<td>-0.10 [-0.16, -0.05]</td>
</tr>
<tr>
<td>CSII</td>
<td>7</td>
<td></td>
<td>27.1 %</td>
<td>-0.20 [-0.27, -0.12]</td>
</tr>
<tr>
<td>T2DM</td>
<td>5</td>
<td></td>
<td>100.0 %</td>
<td>-0.03 [-0.11, 0.04]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypoglycemia</th>
<th>Analogues (N)</th>
<th>Regular (N)</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1DM</td>
<td>2131</td>
<td>2135</td>
<td>100.0 %</td>
<td>-0.23 [-1.14, 0.69]</td>
<td></td>
</tr>
<tr>
<td>T2DM</td>
<td>1302</td>
<td>1315</td>
<td>100.0 %</td>
<td>-0.17 [-0.46, 0.12]</td>
<td></td>
</tr>
</tbody>
</table>


RAIA vs. Human Insulin
Timing relative to meals

- Clinical trials may not capture typical use
- RAIA improve treatment satisfaction and quality of life

Rave et al. Diabetes Care 2006;29(8):1812-1817
Home et al. Diabetes Obes Metab. 2012;14(9):780-8
Limitations of Prandial Insulin

- RAIAs are still absorbed too slowly and duration is still too long to achieve optimal control of PPG
- *Inadequate for closed loop insulin delivery*

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### Factors Known to Influence Absorption and Action of Subcutaneously Injected Insulin

<table>
<thead>
<tr>
<th>Insulin preparation</th>
<th>Differences between injection sites</th>
<th>Changes on the injection site</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dose</td>
<td>• Injection site (intramuscular versus SC)</td>
<td>• Temperature</td>
</tr>
<tr>
<td>• Physical status (soluble or suspension)</td>
<td>• Injection depths</td>
<td>• Physical activity</td>
</tr>
<tr>
<td>• Concentration</td>
<td>• Anatomical region of injection</td>
<td>• Substances known to increase local blood flow</td>
</tr>
<tr>
<td>• Volume</td>
<td>• Lipodystrophy</td>
<td>• Massage</td>
</tr>
<tr>
<td>• Species</td>
<td></td>
<td>• Hypoglycemia</td>
</tr>
<tr>
<td>• Shaking</td>
<td></td>
<td>• Ketoacidosis</td>
</tr>
</tbody>
</table>

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Heinemann et al. J. Diabetes Sci Tech 2012
Approaches for Ultrafast-acting Insulins

<table>
<thead>
<tr>
<th>Mechanical</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase local blood flow: warming</td>
<td>Additives that promote monomers: EDTA, citric acid</td>
</tr>
<tr>
<td>Inhalation</td>
<td>Additives that increase blood flow</td>
</tr>
<tr>
<td>Intradermal</td>
<td>Novel RAIA</td>
</tr>
<tr>
<td>Wider application: jet spray, enzyme alteration of ECM</td>
<td>Additives that facilitate dispersion: hyaluronidase</td>
</tr>
</tbody>
</table>

Heinemann et al. J. Diabetes Sci Tech 2012

Conclusions

- Prandial insulin is often necessary in patients with T2DM but is associated with more weight gain and hypoglycemia
- Prandial insulin should be individualized to fit the needs and capabilities of the patient
- Newer insulin formulations provide opportunities for improving glycemic control and greater treatment satisfaction
Case 1

- Your patient is seen in follow-up. She is now taking 3 injections of rapid acting insulin per day and is adherent.
- What advantage would carb counting provide?
  a) Lower insulin requirements
  b) Less weight gain
  c) Less hypoglycemia
  d) a+b
  e) b+c