Type 1 Diabetes
It's not just insulin deficiency

Elizabeth T. Rosolowsky, MD, MPH, FAAP, FRCPC
Pediatric Endocrinologist
Assistant Professor, Department of Pediatrics
University of Alberta
Paul Cezanne Still Life with Fruit Basket
A Masterpiece of Perspective

Erie Loran Cezanne’s Composition
Outline of Talk

* Anatomy of pancreatic islet cells.
* Neighbor-to-neighbor (paracrine) effects of islet cells on one another and how they affect blood glucose levels.
* Dysregulation of paracrine interactions among α and β cells in T1DM.
* Role of gut-hormone Glucagon-Like Peptide-1 in regulating post-meal blood glucose levels.
* Non-insulin approaches to curbing glycemic fluctuations:
  * Gastric emptying rate
  * Amylin
  * Incretins (Glucagon-Like Peptide 1)
Anatomy of Pancreas
**Alpha, Beta, Delta Cells**

- **Alpha cells** → Glucagon
- **Beta cells** → Insulin
- **Delta cells** → Somatostatin
Paracrine Interactions

- Alpha cells (glucagon)
- Beta cells (insulin)
- Delta cells (somatostatin)
- Glucagon
- Somatostatin
- Insulin
- Glucagon network

© 2008 Encyclopædia Britannica, Inc.
Actions of Insulin v. Glucagon

**Insulin**
- **Storage of Glucose:**
  - Glycogen replenished
  - Fat replenished
  - Protein replenished

**Glucagon**
- **Production of Glucose:**
  - Fat breakdown
  - Glycogen breakdown
  - New glucose made
Insulin lowers blood glucose. Glucagon raises blood glucose.

- Feeding Promotes Fuel Storage
- Fasting Promotes Fuel Production
Relationship among Blood Glucose, Insulin, and Glucagon

Unger and Orci PNAS 2010
Normal Range of Blood Glucose

Unger and Orci PNAS 2010
Confocal Microscopy of Alpha and Beta Cells

Unger and Orci PNAS 2010
1st-Phase Insulin Response

Loss of 1st-Phase Insulin Response in Diabetes Mellitus

Kahn Seminars in Cell & Developmental Biology 2004
Type 1 DM: Paradoxical \( \uparrow \) in Glucagon Following Meal

Unger and Orci PNAS 2010

14 mmol/L
Can giving insulin stop post-meal rise in glucagon?

Amount of insulin needed to suppress post-meal rise in glucagon is 50x amount needed to glucoregulate at peripheral tissues!
Erratic High and Low BGs in T1DM

- There is paradoxical ↑ in glucagon following a meal.
- This excess glucagon cannot be adequately suppressed by insulin alone.

What else can be done?

Unger and Orci PNAS 2010
Leptin Reduces Glycemic Fluctuations

via suppression of glucagon

Wang PNAS 2010
Gastric Emptying Rate

- Speed of movement of stomach contents from stomach to intestine.
- Influenced by volume and composition of food.
- Influences how quickly blood glucose rises after a meal.

Graphic from Lupus International
Amylin

* Islet Amyloid Polypeptide (IAPP)

* Hormone made by β-cell and co-secreted with insulin.

* Complements actions of insulin:
  * Suppresses glucagon
  * Slows gastric emptying
  * Affects satiety centres in brain

From DiabesityDigest.com
Co-secretion of Amylin and Insulin

Amylin Pharmaceuticals
Diabetes Teaching Centre of UCSF
Deficiency of Amylin in Diabetes

Fineman Diabetologia 1995
Pramlintide (Symlin ®)

Human Amylin

Amide-YTNSVNTNSG

Pramlintide (25, 28, 29 Pro-h-amylin)

Amide-YTNSVNTNSG

Buse Clin Diab 2002
Pramlintide Effects: Gastric Emptying and Glucagon

Pramlintide Effects: Glucose Excursions

Weyer Diabetes Care 2003
Pramlintide Effects: HbA1c, Insulin Dose, Weight

- A decrease in HbA1c of about 0.5%
- A decrease in amount of insulin used
- A decrease in weight of about 1 kg

Pramlintide Use in Adolescents with T1DM

Incremental Glucose AUC\(_{0-3h}\)
- Placebo: 217 ± 56 mg·h/mL
- Pramlintide (15μg): 129 ± 43 mg·h/mL
- Pramlintide (30μg): 132 ± 37 mg·h/mL

Incremental Glucagon AUC\(_{0-3h}\)
- Placebo: 35 ± 9 pg·h/mL
- Pramlintide (15μg): 4 ± 7 pg·h/mL
- Pramlintide (30μg): 5 ± 7 pg·h/mL
Pramlintide (Symlin ®)

- In 2005, FDA approved pramlintide as adjunctive therapy in adults with either T1DM or T2DM receiving meal-time insulin.
- Given as subQ injections with meals (pens or vials).
- Not yet approved for children or adolescents with T1DM.
- Major side effects: nausea, hypoglycemia
- Contraindications: gastroparesis, hypoglycemic unawareness
- Risk Minimization Action Plan for 3 areas of concern: Hypoglycemia, Medication errors with mixing pramlintide and insulin, Off-label use
The Incretin Effect

Glucose given orally provokes a greater insulin response than glucose given through an IV.

Nauck Diabetologia 1986
Glucagon-Like Peptide 1 (GLP-1)

- Made by L-cells of small intestine.
- Thought to be responsible for most of incretin effect on pancreatic β-cell function.
- Also has important effects on other organs.
- Degraded by Dipeptidyl peptidase-4 (DPP-4)

Pratley Rev Diabet Stud 2008
Rationale for GLP-1 Therapy in T1DM

- Even in long-standing diabetes, residual β-cells may still respond to incretins.
- Incretins given to islet cell transplant recipients seem to help islet cells function better.
- GLP-1 levels were associated with increased remission in first year following diagnosis of T1DM in children and adolescents.

Bosi J, CEM 2010
Kaas P, Pediatric Diabetes 2012
GLP-1 Effects: Short-Duration T1DM

120 min

Dupre Diabetes 1981
GLP-1 Effects: Long-duration T1DM

Among GLP-1 group:

- Lower post-prandial blood glucose levels
- Lack of post-prandial paradoxical glucagon rise
- Not much effect on insulin dose

Modified from Behme BMC Endocr Disord 2002
Exendin Effects on Volunteers with T1DM

- Glucose excursions following a meal are reduced.
- Glucagon levels do not rise following a meal.
- Gastric emptying rate is slowed.

Modified from Dupre J CEM 2004
Exenatide (Byetta ®)

- Synthetic version of exendin-4 (like GLP-1, only with longer half-life)

- Approved by Health Canada in 2011 for use in adults with T2DM in conjunction with oral hypoglycemic agents or metformin.

- Is NOT approved for treatment of T1DM or use with insulin.

- Provided as subQ injection twice daily before meals.

- Major side effects: Nausea, hypoglycemia, pancreatitis.
Liraglutide (Victoza ®)

- GLP-1 analogue, available in pre-filled pen.
- Health Canada approved since 2010 for use as single daily injection in treatment of adults with T2DM using metformin +/- sulfonylurea.
- Major warning: ↑’d risk thyroid C-cell tumors in rodents, unclear association in humans.
- Increased attention being paid to its potential complimentary role in T1DM therapy:
  - A study of 14 adults with T1DM
  - Intensification of insulin via MDI or pump prior to starting liraglutide.
  - All required to wear Continuous Glucose Monitors.

Varanasi European J Endocrinology 2011
Insulin Therapy, with Liraglutide
Overall Results of Liraglutide Study

- 8 participants who used liraglutide (0.6 to 1.8 mg s.c. daily) for average 24 weeks:
  - Lower fasting glucose levels and lower overall blood glucose levels → HbA1c fell from 6.5 to 6.1%.
  - Average weight loss 4.5 kg (~1.5 to 7.5).
  - No significant increase in hypoglycemia before or during liraglutide treatment.
  - Side effects: headache, nausea, constipation.

Varanasi European J Endocrinology 2011
Other Non-Insulin Therapies

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin (Glucophage ®, Glumetza ®, Fortamet ®, etc.)</td>
<td>Insulin sensitizer; potential cardioprotective effects (REMOVAL study)</td>
</tr>
<tr>
<td>Sitagliptin (Januvia ®)</td>
<td>DPP-4 inhibitor, thus lengthens action of GLP-1</td>
</tr>
<tr>
<td>Metreleptin ®</td>
<td>Suppresses glucagon secretion</td>
</tr>
<tr>
<td>Dapagliflozin (FORXIGA ®)</td>
<td>Sodium-glucose co-transporter-2 inhibitor, reduces glucose absorption in kidney</td>
</tr>
</tbody>
</table>

George and McCrirmon Diab Med 2012
Other Spokes on the Wheel

- Exercise
- Family & Friends
- Goal-Setting
- Neural-Hormonal Interactions
- Medical Nutrition Therapy
- Mental Health
- Communication
- Brain-Body Connection
Paradoxical increase in post-meal glucagon exacerbates hyperglycemia.

Insulin injections themselves cannot offset this problem.

Amylin is also deficient in T1DM. Pramlintide, a synthetic version, can suppress post-meal glucagon, slow gastric emptying, suppress appetite.

GLP-1, an incretin, can also suppress glucagon and augment insulin release in response to food. GLP-1 might also promote β-cell growth and inhibit cell loss.