Artificial Pancreas, shortly close to home?

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Disclosure statement


1. Scholarship: FRQ-S senior (Scholarship; 2011-2015)
5. Consumable gift (in Kind): Animas, Medtronic, Roche
6. Unrestricted grants for clinical and educational activities: Eli Lilly Lifescan, Medtronic, Merck, Novo Nordisk, Sanofi
7. Patent: T2D risk biomarkers
8. Declaration of invention: Artificial pancreas & extending life of catheters

Red highlights products discussed in that presentation (mainly off-label), direct financial support & patents
Objectives

• Rapid overview of remaining barriers for patients with T1D

• Highlight artificial pancreas concept (Closed-loop glucose control)

• Summarize main available data with **single** hormone artificial pancreas

• Summarize main available data with **dual** hormone artificial pancreas

• Summarize main available data **comparing** single and dual hormone artificial pancreas
2015: mean A1c according to age

*≤2 years old and ≥80 years old are pooled.

2015: severe hypoglycemic episodes according to age

1/6 to 1/20 persons with T1D experience severe hypoglycemia each year

*Seizure or Loss of Consciousness: 1 or More Events in 12 Months

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Percentage of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>5%</td>
</tr>
<tr>
<td>6 to 12</td>
<td>4%</td>
</tr>
<tr>
<td>13 to 17</td>
<td>5%</td>
</tr>
<tr>
<td>18 to 25</td>
<td>7%</td>
</tr>
<tr>
<td>26 to 30</td>
<td>9%</td>
</tr>
<tr>
<td>30 to 49</td>
<td>11%</td>
</tr>
<tr>
<td>50 to 65</td>
<td>13%</td>
</tr>
<tr>
<td>&gt;=65</td>
<td>16%</td>
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</tbody>
</table>

Could technology help to overpass barriers for optimal glucose control? « Better, safer, simpler »

HYPOGLYCEMIA
Daily acute
Physical & psychological consequences

HYPERGLYCEMIA
Daily long term
Micro & macrovascular complications

CGM
Continuous Glucose Monitoring

CSII “pump”
Continuous Subcutaneous Insulin Infusion
Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia in patients with documented nocturnal hypoglycemia

Glycated Hemoglobin

<table>
<thead>
<tr>
<th></th>
<th>At randomization</th>
<th>At 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold-Suspend Group</td>
<td>7.26±0.71</td>
<td>7.14±0.77</td>
</tr>
<tr>
<td>Control Group</td>
<td>7.24±0.67</td>
<td>7.21±0.77</td>
</tr>
</tbody>
</table>

Mean AUC for Nocturnal Hypoglycemic Events

<table>
<thead>
<tr>
<th></th>
<th>Run-in phase</th>
<th>Study phase</th>
<th>P &lt; 0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold-Suspend Group</td>
<td>1547±2035</td>
<td>1568±1995</td>
<td>0.60</td>
</tr>
<tr>
<td>Control Group</td>
<td>1406±1950</td>
<td>1484±1810</td>
<td>0.005</td>
</tr>
</tbody>
</table>

A Step Further: Closing the Loop

Glucose Sensor

Control Algorithm

Infusion Pump

SAP
Single-hormone Artificial Pancreas
Insulin only

DAP
Dual-hormone Artificial Pancreas
Insulin & Glucagon
1960
1st Artificial pancreas
SINGLE HORMONE AP VS. CSII
3 months adults and pediatrics

Figure 1. Median (interquartile range) of sensor glucose (top panel) and insulin delivery (bottom panel) during adults day- and-night closed-loop study (A), and children and adolescents overnight closed-loop study (B).

Thabit et al NEJM 2015
Single AP: Summary

- Automated outpatients ✓
- Trials up to 3 months ✓!
- Adults & pediatrics ✓
- Compared to sensor augmented pump therapy
  - Glucose time in target: +10–15%
  - Mean blood glucose: -0.8 mmol/L; A1c: -0.4%
  - Hypoglycemia: reduction > no increase

- What about Dual AP?
DUAL HORMONE AP VS. CSII
Dual Hormone AP vs. CSII

Potential advantages
• Further hypoglycemia reduction (safety net)
• Ability to infuse more aggressively insulin

But more complex & costly
• Need stable glucagon
• Dual chamber pump
• Potential safety issues

Trade-off between benefits and added complexity

AP: artificial pancreas; CSII: continuous subcutaneous insulin infusion.
Dual Hormone AP: Evening & Overnight (15h) Control in Adults

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Closed-loop</th>
<th>CSII</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of time in target range</td>
<td>71 (46 to 88)</td>
<td>57 (25 to 72)</td>
<td>0.003</td>
</tr>
<tr>
<td>% of time &lt;4.0 mmol/L</td>
<td>0.0 (0.0 to 3.0)</td>
<td>10.2 (0.0 to 13.0)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

AP: artificial pancreas; CRC: clinical research centre; CSII: continuous subcutaneous insulin infusion.
Dual Hormone AP: 4 Days, Automated Glucose Control in Adults & Pediatrics

Mean Glucose Levels in Adults

**A** Mean Glucose Levels in Adults

- **Bionic pancreas**
- **Control**

Glucose (mg/dl)

Time

6 P.m. | Midnight | 6 a.m. | Noon | 6 P.m. | Midnight | 6 a.m. | Noon | 6 P.m. | Midnight | 6 a.m. | Noon | 6 P.m. | Midnight | 6 a.m. | Noon | 6 P.m.

Dual AP: Summary

- Automated outpatients
- Night and 24h/7 trials up to 5 days
- Adults & pediatrics
- Compared to sensor augmented pump therapy
  - Glucose time in target: $+10\text{–}15\%$
  - Mean blood glucose: $-0.8\text{–}1.4$ mmol/L
  - Hypoglycemia: reduction $>$ no increase

- Single CL vs. Dual CL comparison?

AP: artificial pancreas; CL: closed loop.
SINGLE HORMONE AP VS. DUAL HORMONE AP
CSII vs. Single AP vs. Dual AP
First head to head comparison

20 Adults & 10 Pediatrics, 3 times 24h

- SAP & DAP reduces hypoglycemia
- DAP provides additional reduction in hypoglycemia
- SAP might be sufficient for hypoglycemia-free overnight control

SAP vs. CSII: \( P=0.00049 \); DAP vs. CSII: \( P=0.00019 \); DAP vs. SAP: \( P=0.018 \).

SAP: single-hormone artificial pancreas; DAP: dual-hormone artificial pancreas.

CSII vs. Single AP vs. Dual AP

First pediatric & outpatient head to head comparison

- **CSII**
- **Single AP (insulin)**
- **Dual AP (insulin & glucagon)**
- Pediatric (n=33)
  - 8–17 years
- 3 nights/intervention
  - 9 nights/kids
  - >290 nights

CSII vs. Single AP vs. Dual AP

Hypoglycemia (%)

Time in Hypoglycemia (<4.0 mmol/L)

Number of hypoglycemic events (< 3.1 mmol/L)

<table>
<thead>
<tr>
<th></th>
<th>CSII</th>
<th>Single AP</th>
<th>Dual AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of hypoglycemic events</td>
<td>15</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

CSII vs. SAP: P=0.32; SAP vs. DAP: P=0.032; DAP vs. CSII: P=0.0048.
CSII: continuous subcutaneous insulin infusion; AP: artificial pancreas.
CSII vs. SAP vs. DAP

60 consecutive hours outpatients

22 Adults

Time < 4.0 mmol/L

- CSII: 108 min
- SAP: 61 min
- DAP: 51 min

Time < 3.5 mmol/L

- CSII: 50 min
- SAP: 36 min
- DAP: 13 min

Number of hypoglycemia

- CSII: 30
- SAP: 14
- DAP: 6

Haidar H & al IDF 2015
SAP vs. DAP
Exercise and hypoglycemia

17 patients 1 h exercise continuous or intermittent

% Time in Hypoglycemia (< 4.0 mmol/L)

% temps dans la cible (4.0 à 10.0 mmol/L)

% patients with treated hypoglycemia

31.2

9

CSII: continuous subcutaneous insulin infusion; SAP: single-hormone artificial pancreas; DAP: dual-hormone artificial pancreas.
1. Haidar H e& Ladouceur M MS in preparation
Single AP vs. Dual AP: Summary

• Automated studies (Health Canada submission ongoing)

• Night and 24h trials up to 60h hours

• Adults & pediatrics

• DAP and/or SAP
  ▪ Glucose time in target: \( \approx +10\% \) (DAP & SAP Vs CSII)
  ▪ Mean blood glucose: no change vs -0.3 mmol/L (overnight with DAP)
  ▪ Hypoglycemia: 50% additional reduction DAP vs. SAP

Exercise: DAP superior to SAP

Hypo-unaware (overnight): DAP = SAP
No carbohydrate counting?
No meal announcement?

SIMPLYFYING MEALS
Rationale for Carbohydrate Counting: CHO is the Main Determinant of PPG glucose excursion

Despite numerous factors:
• Glycemic index
• Fibre content
• Gastric emptying
• etc.

Better PPG $\rightarrow$ Better A1C

CHO: carbohydrate; PPG: postprandial glucose

Precision of Carbohydrate Estimation is Important, But a Difficult Task

Over 448 meals, the mean meal contains: 72.4 g

In youth, low impact of errors <10–15 g

TIT: Time In Target

Alleviate the Carbohydrate Counting Burden with DAP

Current & Future

Stable Glucagon
Is Artificial Pancreas Ready for Prime Time?

• NO! Not yet?
  ▪ Extremely promising short-term results
  ▪ Significant potential to improve overall control while minimizing hypoglycemia and simplifying treatment
  ▪ Probable step-by-step market introduction, with the first version still needing patients to inform algorithm about meal & exercise
  ▪ Interest of adjunct therapy (GLP-1 receptor agonists; SGLT-2 inhibitors, etc.) and new faster-acting insulin under investigation
  ▪ Could also be useful for some patients with T2DM
    ▪ Early: inducing remission; later reducing hypoglycemic risk & improving mean control
  ▪ Rapidly progressing field
    ▪ Needs: integration of components, dual chamber pump, stable glucagon
  ▪ Other applications: recurrent hypo with DAP (e.g. post-bariatric surgery)

T2DM: type 2 diabetes mellitus.
Financement
Main students & Collaborators

IRCM (Current)
- Ahmad Haidar
- Virginie Messier
- Nadine Taleb
- Véronique Gingras
- Maryse Dallaire
- Jennifer René
- Corinne Supère
- Catherine Leroux
- Ali Emani
- Mohamed Smaoui

Cr CHUM
- J-L Chiasson
- M Ladouceur (Biostat)

McGill
- Laurent Legault
- Benoit Boulet

University of Toronto
- Bruce Perkins
DU MERCREDI 9 MARS
AU SAMEDI 12 MARS 2016

2016 DIABETES UPDATE

Nouvel endroit en 2016 :
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Subash Varma, M.D.
Jean-François Yelle, M.D.
Bernard Zimmerman, M.D.

INSCRIVEZ-VOUS DÈS Aujourd’hui sur
WWW.DIABETESUPDATE.CA

Ne manquez pas la chance de participer à ce congrès de deux jours et demi qui transformera votre pratique sur le diabète.
Par l’entremise de séances plénières, d’ateliers interactifs et d’études de cas, les conférenciers renommés discuteront de l’information la plus récente sur la prévention et le traitement du diabète et de ses complications, selon la perspective du mode de vie et celle des médicaments.
Veillez prendre note que les conférences seront présentées en anglais exclusivement.

Ce programme a été rendu possible grâce à une subvention à visée éducative de : Abbott, AstaZeneca, Boehringer Ingelheim B Lilly, Janssen, Merck, Sanofi et Servier.