Clinical News and Innovation in Type 1 Diabetes and Technology

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Birmingham
• Adjunctive therapy to insulin
• Accurate diagnosis of T1D
• Early intensive treatment
• Technology
  – Glucose sensing
  – Insulin delivery with sensor augmentation
  – Artificial pancreas
• The post code lottery that is T1D care in the UK
• Suggested way forward
Adjunctive therapy to insulin
# Getting to target in T1D?

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Under 40</td>
<td>40 to 64</td>
<td>65 to 79</td>
</tr>
<tr>
<td>HbA&lt;sub&gt;1c&lt;/sub&gt; &lt;48mmol/mol (6.5%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.7%</td>
<td>6.7%</td>
<td>8.6%</td>
</tr>
<tr>
<td>HbA&lt;sub&gt;1c&lt;/sub&gt; &lt;58mmol/mol (7.5%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24.8%</td>
<td>26.0%</td>
<td>35.5%</td>
</tr>
<tr>
<td>HbA&lt;sub&gt;1c&lt;/sub&gt; &lt;86mmol/mol (10.0%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>77.5%</td>
<td>84.4%</td>
<td>91.4%</td>
</tr>
<tr>
<td>BP ≤140/80&lt;sup&gt;b&lt;/sup&gt;</td>
<td>78.1%</td>
<td>70.3%</td>
<td>71.7%</td>
</tr>
<tr>
<td>Cholesterol &lt;4mmol/L</td>
<td>22.3%</td>
<td>28.4%</td>
<td>41.6%</td>
</tr>
<tr>
<td>Cholesterol &lt;5mmol/L</td>
<td>64.1%</td>
<td>70.4%</td>
<td>81.5%</td>
</tr>
<tr>
<td>Meet all treatment targets&lt;sup&gt;c&lt;/sup&gt;</td>
<td>14.7%</td>
<td>14.7%</td>
<td>22.4%</td>
</tr>
</tbody>
</table>

National Diabetes Audit
# Table 3. Adjusted Hazard Ratios for Death from Any Cause and Death from Cardiovascular Causes among Patients with Type 1 Diabetes versus Controls, According to Time-Updated Mean Glycated Hemoglobin Level and Renal Disease Status, Model 3.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death from Any Cause</th>
<th>Death from Cardiovascular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-updated mean glycated hemoglobin level — no. of events/total no.</td>
<td>7386/200,539</td>
<td>2326/200,539</td>
</tr>
<tr>
<td>Reference group (controls)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>≤6.9%</td>
<td>2.36 (1.97–2.83)</td>
<td>2.92 (2.07–4.13)</td>
</tr>
<tr>
<td>7.0–7.8%</td>
<td>2.38 (2.02–2.80)</td>
<td>3.39 (2.49–4.61)</td>
</tr>
<tr>
<td>7.9–8.7%</td>
<td>3.11 (2.66–3.62)</td>
<td>4.44 (3.32–5.96)</td>
</tr>
<tr>
<td>8.8–9.6%</td>
<td>3.65 (3.11–4.30)</td>
<td>5.35 (3.94–7.26)</td>
</tr>
<tr>
<td>≥9.7%</td>
<td>8.51 (7.24–10.01)</td>
<td>10.46 (7.62–14.37)</td>
</tr>
</tbody>
</table>
Options for glucose lowering agents (other than than insulin) in T1D

<table>
<thead>
<tr>
<th>Currently licensed</th>
<th>Not licensed but promising</th>
<th>Not licensed but potential in selected patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>SGLT inhibitors</td>
<td>Pioglitazone</td>
</tr>
<tr>
<td>Metformin</td>
<td>GLP1 agonists</td>
<td>Acarbose</td>
</tr>
<tr>
<td>Pramlintide (not licensed in UK)</td>
<td></td>
<td>Bariatric surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DPP IV inhibitors</td>
</tr>
</tbody>
</table>
Effect of 10mg Dapagliflozin in a T1D patient

<table>
<thead>
<tr>
<th></th>
<th>Pre - DAPA</th>
<th>During DAPA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Range</strong></td>
<td>2.2 - 18.8 mmol/L</td>
<td>2.2 – 16.1</td>
</tr>
<tr>
<td><strong>% High</strong></td>
<td>12%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>% Low</strong></td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Num high periods</strong></td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td><strong>Num low periods</strong></td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td><strong>CGM Std Dev</strong></td>
<td>3.2 mmol/L</td>
<td>2.2 mmol/L</td>
</tr>
<tr>
<td><strong>Insulin TDD</strong></td>
<td>43.6 U</td>
<td>33.9 U</td>
</tr>
</tbody>
</table>
DEPICT 1 (Dapagliflozin) | Global **inTandem3** (Sotagliflozin)
---|---
HbA1c reduction: 0.4-0.5% | HbA1c reduction: 0.5%
Daily insulin: 10% | Daily insulin: 9%
Body weight: 3Kg | Body weight: 3Kg
SBP 3-6 | SBP 3.5
SH – NS | SH – NS
DKA - NS | DKA 5x
GU infection 4x | GU infection 3x

**Dapa T2D**
- HbA1c: 0.5%
- Weight: 2Kg
- SBP: 4mmHg
- DBP: 2mmHg
European and Israeli inTandem2

782 participants, DKA 2-3%
<table>
<thead>
<tr>
<th>Current state of play</th>
<th>If licensed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AZ Dapagliflozin for T1D</strong></td>
<td>Who prescribes?</td>
</tr>
<tr>
<td>EMEA decision late 2018?</td>
<td>The importance and practicalities of education</td>
</tr>
<tr>
<td>NICE decision mid 2019?</td>
<td>DKA risk subgroups: females? CSII?</td>
</tr>
<tr>
<td><strong>Sanofi Sotagliflozin for T1D</strong></td>
<td>DKA risk does not decline with therapy duration</td>
</tr>
<tr>
<td>EMEA decision late 2018?</td>
<td></td>
</tr>
</tbody>
</table>
Accurate diagnosis of T1D
Differentiating between T1D and T2D is challenging

- 86% accurate in white European
- 70% accurate in south Asian

Hope 2016, Thomas 2018
Do not measure C-peptide and/or diabetes-specific autoantibody titres routinely to confirm type 1 diabetes in adults.

Consider further investigation in adults that involves measurement of C-peptide and/or diabetes-specific autoantibody titres if:

- type 1 diabetes is suspected but the clinical presentation includes some atypical features
  - or
- type 1 diabetes has been diagnosed and treatment started but there is a clinical suspicion that the person may have a monogenic form of diabetes
  - or
- classification is uncertain, and confirming type 1 diabetes would have implications for availability of therapy
Clinical cases can be challenging

- 20yr old South Asian
- Strong family history of T2D
- Diagnosed with ‘T1D’ whilst on holiday in Pakistan
- Ab negative
- C peptide high
- Not taking insulin for 3 weeks: glucose 7-12mmol/L without ketones
- T1D in Honeymoon?
- T2D?
Primary objective

- To establish diagnostic performance of biomarkers including islet autoantibodies, C-peptide and a genetic risk score in identifying patients with rapid requirement for insulin, alone and in combination with clinical features.

Secondary objectives

- To prospectively validate a clinical prediction model developed from cross sectional datasets in predicting rapid insulin requirement in young onset diabetes.
- To integrate discriminative and additive biomarkers into the clinical prediction model.
- To establish a bio resource for future biomarkers discovery and assessment.
Early intensive treatment for T1D
Glycaemic tracking and importance of early intensive treatment
(4,500 incident cases of UK T1D)

Krishnarajah et al 2018
Exploratory plots - stratified by sex and age

Krishnarajah et al 2018
Conclusions

• Individuals with type 1 diabetes, glycaemic control measured by HbA$_{1c}$ settles onto a long-term ‘track’

• Tracking occurs on average at 4-5 years following diagnosis

• Age at diagnosis modifies both the rate at which individuals settle into their track and the absolute HbA$_{1c}$ tracking level

• Early targeted intervention may impact on long term outcomes

Krishnarajah et al 2018
Technology
Emerging recognition of the value of continuous glucose feedback in the day to day management of glucose

• Flash glucose sensing
• Continuous glucose monitoring
Freestyle Libre
Impact on decision making

- Response to this...
- ...very different to....
Example of how continuous feedback can help

Haemoglobin A1C

Libre started

Courtesy of Emma Wilmot
Real world Libre data

- 51K readers, worldwide
- Average 16 scans/day

T. Dunn, Y. Xu, G. Hayter, Abbott Diabetes Care, ATTD 2017
Cgm is useful in people on MDI (as well as pumps)
Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial

Denise S Feig, Lois E Donovan, Rosa Corcoy, Kellie E Murphy, Stephanie A Arniel, Katharine F Hunt, Elisabeth Asztalos, Jon R R Barrett, J Johanna Sanchez, Alberto de Leiva, Moshe Hod, Lois Jovanovic, Erin Keely, Ruth McManus, Eileen K Hutton, Claire L Meek, Zoe A Stewart, Tim Wysocki, Robert O’Brien, Katrina Ruedy, Craig Kollman, George Tomlinson, Helen R Murphy, on behalf of the CONCEPTT Collaborative Group

- HbA1c improved by 0.19%
- TIR increased from 61% to 68%
- Significant improvement in neonatal outcomes
  - Large for gestational age – 69 to 53%
  - Neonatal hypoglycaemia requiring IV dextrose – 28 to 15%
  - Need for ICU – 43 to 27%
  - 1 day less in hospital
Glucose sensing/monitoring

- Libre – Libre like
- Real time CGM: Dexcom G6, Enlite 3, Medrum
- Implantable sensors: Senseonics
The **dynamic suspend** feature is based on certain criteria: sensor glucose must be within 3.9mmol/L of the low limit and predicted to be 1.1mmol/L above the low limit within 30 minutes AND the pump must not be in the refractory period.

The **dynamic resume** feature is based on certain preset criteria: sensor glucose must be 1.1mmol/L above the preset low limit and predicted to be 2.2mmol/L above within 30 minutes AND insulin must have been suspended for at least 30 minutes.
Other low glucose suspend systems

**t:silm X2™ Insulin Pump**

NEW! Predicts and helps prevent lows with Basal-IQ™ Technology

Tandem pump and Dexcom sensor
US release March 2017
UK release planned Autumn 2018

Real world data from ADA
Lower mean BG
Increased time in range

<table>
<thead>
<tr>
<th></th>
<th>Manual Mode</th>
<th>After Auto Mode start</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
<td>13,906</td>
<td></td>
</tr>
<tr>
<td>Auto Mode Use, %</td>
<td>–</td>
<td>80.05%</td>
</tr>
<tr>
<td>Mean SG, mg/dL</td>
<td>163.53</td>
<td>154.87</td>
</tr>
<tr>
<td>SD SG, mg/dL</td>
<td>54.22</td>
<td>51.04</td>
</tr>
<tr>
<td>Percentage of time in SG ran</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>0.38%</td>
<td>0.31%</td>
</tr>
<tr>
<td>&lt;54</td>
<td>0.60%</td>
<td>0.49%</td>
</tr>
<tr>
<td>&lt;70</td>
<td>2.59%</td>
<td>2.05%</td>
</tr>
<tr>
<td>70–180</td>
<td>63.16%</td>
<td>71.35%</td>
</tr>
<tr>
<td>&gt;180</td>
<td>34.24%</td>
<td>26.60%</td>
</tr>
</tbody>
</table>
Other potential hybrid closed loops

• What is a hybrid closed loop?
• Omnipod Insulet hybrid closed loop
• Diabeloop DBLG1
• Dual hormone (insulin and glucagon)
A way forward
The post code lottery that is T1D care in the UK

- Flash Glucose sensing
- CGM
- Psychology
- Emerging technology
Keeping up with emerging technology

Howard Look
@howardlook

At 7:11p my daughter received her first insulin delivered by a software decision. #OpenAPS #WeAreNotWaiting

7:21 PM - 14 Jan 2016

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A way forward?

- Offer participation in research
- Structured education
- Glucose download facilities
- Transition service
- Pregnancy care
- Flash
- Insulin pumps
- CSII
- Sensor augmented pumps
- Closed loop pumps
- Other approaches to insulin delivery (IP)
- Beta cell replacement

All T1D centres

Regional T1D Hubs
- KPI
- Referral centre for the more complicated patient
- Responsibilities for teaching and training local centres
- Hubs would meet to discuss more difficult patients