Model-based Analysis of the GLP-1 Response Following an Oral Glucose Tolerance Test (OGTT)

Objective
- To gain further insights into the pathophysiology of Type 2 diabetes, by providing description of the GLP-1 response following an oral glucose administration.

Background
- GLP-1 is known as an insulino-tropic hormone, meaning that the insulin response to elevated glucose levels is increased in the presence of this hormone [1].
- The GLP-1 response is increased in the presence of nutrients in the gastrointestinal (GI) tract and thus also following intake of oral glucose.
- It is not clear how dynamics of such a response is changed under pathological conditions e.g. in subjects with impaired glucose tolerance.
- Compared to a standard analysis (AUC and Cmax), a PK/PD model of the response will provide more information regarding dynamics and can easily be used to detect the impact of demographic factors on these.

Methods
- In order to obtain such descriptive indices, a semi-mechanistic model for the GLP-1 response was built using glucose, insulin, and GLP-1 data [2].
- Initially, the glucose absorption rate was estimated only using glucose and insulin concentrations. The estimated glucose absorption rate was used as input to the GLP-1 model [3].

Table 1: Mean (SD) of demographic factors and baseline characteristics. S indicates magnitude on slow GLP-1 response.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Normal</th>
<th>IFG-IGT-T2D</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td></td>
<td></td>
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<tr>
<td>Age (yr)</td>
<td></td>
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<tr>
<td>Fasting plasma glucose [mg·dL⁻¹]</td>
<td>41.77 (11.4)</td>
<td>45.56 (12.7)</td>
<td>42.27 (11.6)</td>
</tr>
<tr>
<td>Fasting plasma insulin [pmol·L⁻¹]</td>
<td>93.02 (8.1)</td>
<td>109.82 (13)</td>
<td>95.26 (10.5)</td>
</tr>
<tr>
<td>GLP1 stimulation - Sa [mg⁻¹]</td>
<td>5.43 (3.1)</td>
<td>11.66 (6.4)</td>
<td>6.26 (4.6)</td>
</tr>
<tr>
<td>GLP1 stimulation - Sa [pmol·L⁻¹]</td>
<td>5.35 (3.3)</td>
<td>4.61 (2.6)</td>
<td>5.26 (3.2)</td>
</tr>
<tr>
<td>Fasting plasma GLP-1 (total) [pmol·L⁻¹]</td>
<td>10.76 (8.7)</td>
<td>13.16 (12.7)</td>
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</tr>
</tbody>
</table>

Table 1: Distribution of subjects and baseline values

Figure 1: (A) Indirect response model relating glucose and insulin dynamics applied for estimation of glucose absorption rate, (B) GLP-1 model using glucose absorption rate as input. Triangles present delay(transit) compartments.

Figure 2: Black =Individual observations, Blue =Mean observations, Red =Population prediction.

Figure 3: S: Fast stimulation component, A: Glucose absorption rate, S: Slow stimulation component.

Results and conclusions
- The final indirect-response model obtained for GLP-1 production following an oral glucose tolerance test included two stimulation components on a zero-order production rate. (Fig. 1)
- The fast stimulation was estimated to arrive prior to glucose absorption, suggesting a neuro-endocrine loop, where nutrients in duodenum stimulates GLP-1 secretion from L-cells in the lower part of GI (ileum). (Fig. 3)

Conclusions
- A semi-mechanistic population model was successfully developed and applied to describe total GLP-1 concentrations over time observed after an OGTT
- The secretion of GLP-1 appears to be stimulated by glucose in two ways: by a fast mechanism driven by glucose dose in the GI and by a slower mechanism driven by glucose absorption rate.
- The model provides a good basis to study influence of demographic factors on individual GLP-1 secretion capabilities.

References

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