Disease progression in the integrated glucose-insulin model in subjects with impaired glucose tolerance

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Conclusion
The disease progression was successfully included in the IGI model to describe differences seen in a population with IGT with or without lifestyle intervention. In particular, insulin dependent glucose clearance improved after intensive lifestyle intervention.

Objective
The objective of this project was to develop the IGI model to include disease progression in subjects with impaired glucose tolerance (IGT).

Introduction
The integrated glucose-insulin (IGI) model was published1–3 describing glucose and insulin after various glucose provocations in healthy subjects and in patients with type 2 diabetes. However, this model currently does not include disease progression from prediabetes, i.e. impaired glucose tolerance, to overt diabetes, which is driven by decreased insulin sensitivity and relative beta cell failure.

Methods

• Study design
The data was obtained from the FDPS substudy as described in Figure 1. The subjects were middle-aged (mean age=53) and overweight (mean BMI=31.5) with IGT.

• Modelling
The IGI model was used to fit FSIGT and OGTT data for baseline until the fourth year, incorporating prior information6 on the parameters.

• Disease progression
The DP model was set to start at 24 hours after the end of baseline study period and was investigated on the pathophysiologically most reasonable parameters, e.g. insulin-dependent glucose clearance (CLGI), insulin first phase secretion (IFST), maximum incretin effect (EMAX) and effect of glucose on it’s own production (GPGR).

The impact of diet and exercise intervention on the DP was investigated. The best model was chosen based on objection function value (OFV), diagnostic plots and visual predictive check (VPC).

Figure 1: Finnish Diabetes Prevention Study (FDPS)1,5

Table 1: Effect of disease progression on IGI model parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IGT**</th>
<th>Healthy†</th>
<th>Type 2 DM2,3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLGI</td>
<td>0.00460</td>
<td>50.9</td>
<td>0.00829</td>
</tr>
<tr>
<td>IFST</td>
<td>118</td>
<td>128</td>
<td>704</td>
</tr>
<tr>
<td>EMAX</td>
<td>1.78</td>
<td>17.7</td>
<td>0.0818*</td>
</tr>
<tr>
<td>CAS50</td>
<td>14.1</td>
<td>136</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviation: CLGI=Insulin-dependent glucose clearance (L/min/mU/L), EMAX=Maximal incretin effect; CAS50=Absorbed glucose at 50% Emax (mg/dL) IFST=First phase insulin secretion (muU) TV-Typical value *linear incretin effect (mg/min) was used instead of Emax function

** The insulin-independent glucose clearance was fixed to the healthy value of 0.0287 L/min

Figure 2: IVGTT IGI Model Structure 1/3

Table 2: Selected parameter estimates differences between IGT, healthy and type 2 diabetes

References

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