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 published[1-3] 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**

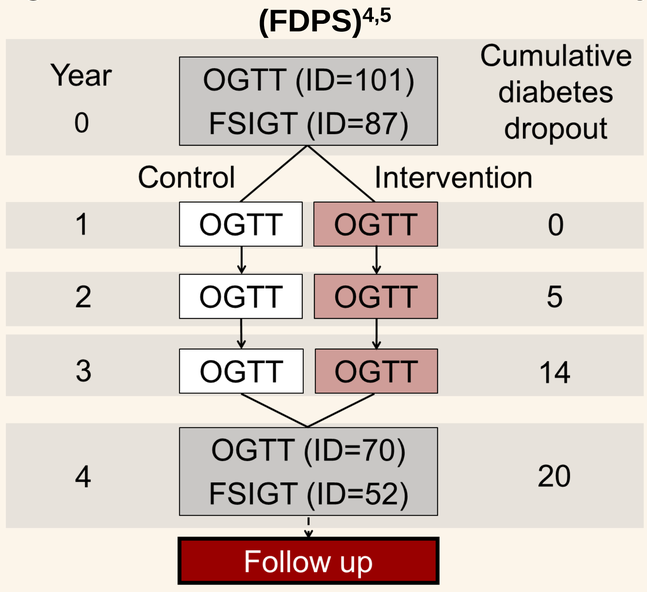
The IGI model was used to fit FSIGT and OGTT data for baseline until the fourth year, incorporating prior information[6] on the parameters.

- **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 (GPRG).

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).

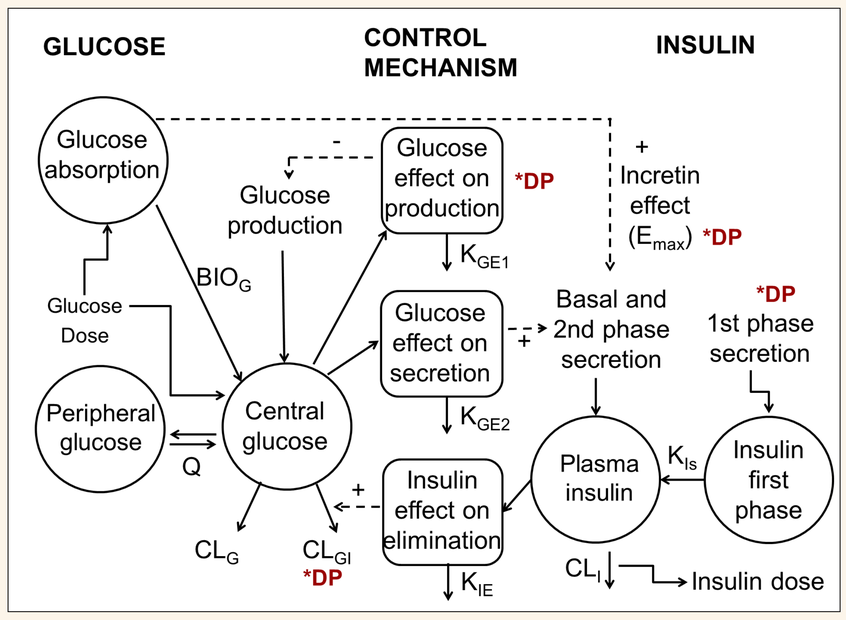
Figure 1: Finnish Diabetes Prevention Study (FDPS)[4,5]



FSIGT = Frequently Sampled Intravenous Glucose Tolerance Test

OGTT = Oral Glucose Tolerance Test

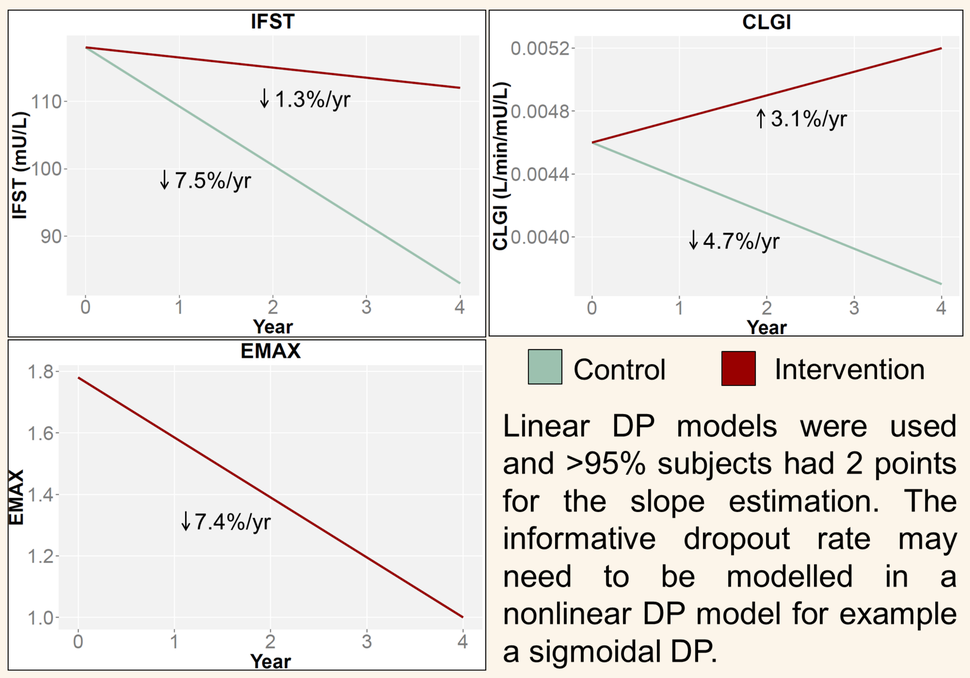
Figure 2: IVGTT IGI Model Structure [1-3]



Disease Progression (DP) = 1 ± THETA(X) * Time (Year)

Results and Discussion

Table 1: Effect of disease progression on IGI model parameters



Linear DP models were used and >95% subjects had 2 points for the slope estimation. The informative dropout rate may need to be modelled in a nonlinear DP model for example a sigmoidal DP.

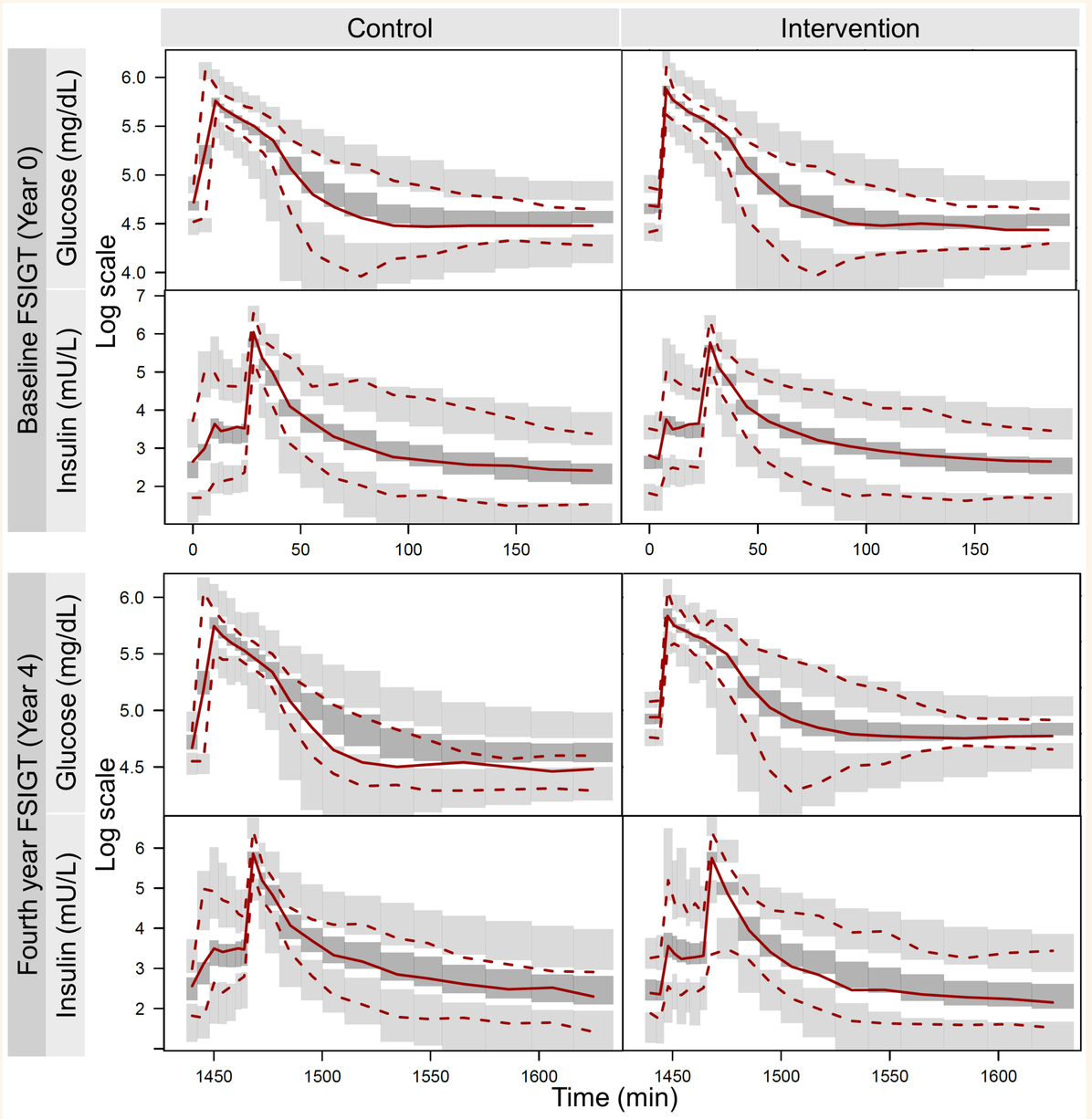
Table 2: Selected parameter estimates differences between IGT, healthy and type 2 diabetes

Parameter	IGT**		Healthy[1]		Type 2 DM[2,3]	
	TV	IIV%	TV	IIV%	TV	IIV%
CLGI	0.00460	50.9	0.00829	53.0	0.00297	53.0
IFST	118	128	704	67.0	-	-
EMAX	1.78	17.7	0.0818*	21.0	1.47	55.0
CA50	14.1	136	-	-	14.8	114

Abbreviation: CLGI-Insulin-dependent glucose clearance (L/min/mU/L), **EMAX**-Maximal incretin effect(-), **CA50**-Absorbed glucose at 50% E_{max} (mg/dL), **IFST**-First phase insulin secretion (mU), **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 3: Visual predictive checks (VPC) for Year 0 and 4



Overall, the model fit was good. The model overprediction the elimination phase of the glucose component for the fourth year FSIGT (control group) might be explained by the presence of feedback effect of insulin on glucose production, the low pre and post hepatic glucose production and the high endogenous and exogenous insulin secretion. The VPCs for yearly OGTT were not shown in the figure, but they were as good as IVGTT.

References

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