Model Based Analysis of Ethnic Differences in Type 2 Diabetes

The present thesis deals with different aspects of population pharmacokinetic/pharmacodynamic (PK/PD) modelling of the glucose homeostatic system. The thesis consist of a summary report and four scientific research papers. A description of the main topics covered in the thesis is given in the summary report. This includes a short introduction to the mathematical methods applied in the thesis, followed by an outline of the physiological and pathological aspects of the glucose homeostatic system and how to obtain diagnostic indices for characterising the condition of the system. Finally an overview of ethnic differences in type 2 diabetes (T2D) is given, which relates to the subject of the last 2 papers included in the thesis.

One of the main objectives of the thesis was to investigate possible ethnic differences between development of T2D in Caucasian and Japanese and investigate the applicability of stochastic differential equations (SDEs) and non-linear mixed effects (NLME) models for such an assessment. One way to perform such an investigation is to characterise the pathophysiology of the two groups at different stages of disease progression. For T2D this involves a characterisation of the glucose homeostatic system, which is a complex feedback system mainly involving mainly organs such as the liver and the pancreas, the hormones insulin and glucagon, and the carbohydrate glucose.

As for any other dynamical system, a proper characterisation at non-steady state, requires a proper input to the system. This input must reflect the circumstances in which one wants to draw conclusions. In this thesis the intake of oral glucose, which closely resembles the intake of food under daily living has been applied.

Mathematical modelling of such complex physiological phenomena as the glucose homeostatic system will usually be based on both insight into the system and experimental data. Through estimation techniques, free parameters in the models are estimated and can be related directly to behaviour of the system. These semi-physical (grey box) models are well suited for understanding the system, although in many cases they are not able to fully describe the systematic behaviour observed in the applied data sets. This issue can be addressed through an inspection of the autocorrelation function (ACF) of residuals and the description can be improved by switching to the use of stochastic differential equations (SDEs) or another improved description of residuals.

For characterising disease progression in Caucasian and Japanese, established models that include parameters for insulin sensitivity and beta-cell function were implemented in a non-linear mixed-effects setting with ODEs. Based on the ACF of residuals it was clear that the two models provide a good, although not perfect, description of the systematic variation in the analysed data sets. Based on this the models were extended to SDE models for improved description of residuals. Using the SDE models it was not possible to obtain convergence with the full covariate models so the results presented in the thesis mainly originate from the ODE models. This also caused a more fair comparison with the well-established single-subject models implemented using ODEs.

Previous research have stated the importance of the gut hormone glucagonlikepeptide-1 (GLP-1) as determinant for normal beta-cell function. Based on this a population PK/PD model for secretion of (GLP-1) following an oral glucose tolerance test (OGTT) was developed. This model can be used as a tool to analyse potential differences in the secretion capabilities of GLP-1 between subjects. ACF of residuals did not show any signs of strong serial correlation, and the model was thus not implemented using SDEs.

Assessment of simple and model-based measures for insulin sensitivity and beta-cell function in Japanese and Caucasian subjects stratified according to normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and T2D showed that Japanese in general have higher insulin sensitivity and lower beta-cell function compared to Caucasians. In spite of this, the pattern going from NGT to T2D appeared similar in the two cohorts and the majority of the difference in insulin sensitivity and beta-cell function, measured by simple insulin based measures, could be explained by difference in body size (BMI). This was supported by Forest plots of covariate effects obtained from population models, in general indicating that race had no clinical relevant effect on either the insulin sensitivit y or the beta-cell function when measures for obesity (android fat mass or BMI) was taken into account.

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Predictive performance for population models using stochastic differential equations applied on data from an oral glucose tolerance test

Several articles have investigated stochastic differential equations (SDEs) in PK/PD models, but few have quantitatively investigated the benefits to predictive performance of models based on real data. Estimation of first phase insulin secretion which reflects beta-cell function using models of the OGTT is a difficult problem in need of further investigation. The present work aimed at investigating the power of SDEs to predict the first phase insulin secretion (AIR(0-8)) in the IVGTT based on parameters obtained from the minimal model of the OGTT, published by Breda et al. (Diabetes 50(1): 150-158, 2001). In total 174 subjects underwent both an OGTT and a tolbutamide modified IVGTT. Estimation of parameters in the oral minimal model (OMM) was performed using the FOCE-method in NONMEM VI on insulin and C-peptide measurements. The suggested SDE models were based on a continuous AR(1) process, i.e. the Ornstein-Uhlenbeck process, and the extended Kalman filter was implemented in order to estimate the parameters of the models. Inclusion of the Ornstein-Uhlenbeck (OU) process caused improved description of the variation in the data as measured by the auto-correlation function (ACF) of one-step prediction errors. A main result was that application of SDE models improved the correlation between the individual first phase indexes obtained from OGTT and AIR(0-8) ($r = 0.36$ to $r = 0.49$ and $r = 0.32$ to $r = 0.47$ with C-peptide and insulin measurements, respectively). In addition to the increased correlation also the properties of the indexes obtained using the SDE models more correctly assessed the properties of the first phase indexes obtained from the IVGTT. In general it is concluded that the presented SDE approach not only caused autocorrelation of errors to decrease but also improved estimation of clinical measures obtained from the glucose tolerance tests. Since, the estimation time of extended models was not heavily increased compared to basic models, the applied method is concluded to have high relevance not only in theory but also in practice.

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Authors: Møller, J. B. (Intern), Overgaard, R. (Ekstern), Madsen, H. (Intern), Hansen, T. (Ekstern), Pedersen, O. (Ekstern), Ingwersen, S. (Ekstern)
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Phd Student:
Møller, Jonas Bech (Intern)
Supervisor:
Ingwersen, Steen Hvass (Ekstern)
Overgaard, Rune Viig (Intern)
Main Supervisor:
Madsen, Henrik (Intern)
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Brockhoff, Per B. (Intern)
Jacqmin, Philippe (Ekstern)
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