European Journal of Pharmaceutical Sciences 104 (2017) 417–423

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

# Impact of demographics and disease progression on the relationship between glucose and HbA1c☆

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ARTICLE INFO

*Keywords:*
Diabetes mellitus
Glycated haemoglobin
Meta-analysis
Modelling
HbA1c

ABSTRACT

*Context:* Several studies have shown that the relationship between mean plasma glucose (MPG) and glycated haemoglobin (HbA1c) may vary across populations. Especially race has previously been referred to shift the regression line that links MPG to HbA1c at steady-state (Herman & Cohen, 2012).
*Objective:* To assess the influence of demographic and disease progression-related covariates on the intercept of the estimated linear MPG-HbA1c relationship in a longitudinal model.
*Data:* Longitudinal patient-level data from 16 late-phase trials in type 2 diabetes with a total of 8927 subjects was used to study covariates for the relationship between MPG and HbA1c. The analysed covariates included age group, BMI, gender, race, diabetes duration, and pre-trial treatment. Differences between trials were taken into account by estimating a trial-to-trial variability component.
*Participants:* Participants included 47% females and 20% above 65 years. 77% were Caucasian, 9% were Asian, 5% were Black and the remaining 9% were analysed together as other races.
*Analysis:* Estimates of the change in the intercept of the MPG-HbA1c relationship due to the mentioned covariates were determined using a longitudinal model.
*Results:* The analysis showed that pre-trial treatment with insulin had the most pronounced impact associated with a 0.34% higher HbA1c at a given MPG. However, race, diabetes duration and age group also had an impact on the MPG-HbA1c relationship.
*Conclusion:* Our analysis shows that the relationship between MPG and HbA1c is relatively insensitive to covariates, but shows small variations across populations, which may be relevant to take into account when predicting HbA1c response based on MPG measurements in clinical trials.

## 1. Introduction

In type 2 diabetes mellitus it is essential to keep glucose levels in the normo-glycaemic range to prevent hypo- and hyperglycaemia, and related complications. Glycaemic control is commonly maintained by monitoring fasting plasma glucose (FPG). In early clinical drug development and short-term clinical trials plasma glucose is the preferred biomarker. Plasma glucose has a fast turnover rate and it is thus possible to assess drug effects within hours or days. However, plasma glucose is also highly variable and sensitive to glucose intake. Furthermore, since plasma glucose values can vary considerably from day to day, it is not a reliable biomarker for assessing long-term efficacy in clinical trials. For sustained glucose control, the preferred biomarker is glycated haemoglobin (HbA1c), which is considered the primary efficacy endpoint by regulators (EMA, May 2012; FDA, February 2008) and several studies have explored the relationship between HbA1c and clinical outcomes, e.g. cardiovascular outcomes (Meigs et al., 1996). HbA1c is insensitive to daily fluctuations due to food intake or circadian variation, which makes it the gold standard biomarker in clinical drug development within diabetes. However, the turnover rate

☆ Disclosure Statement: Anetta Claussen, Jonas B. Møller, Niels R. Kristensen, Søren Klim, and Steen H. Ingwersen are all employees of Novo Nordisk A/S and/or own stocks in the company.

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http://dx.doi.org/10.1016/j.ejps.2017.04.006
Received 20 October 2016; Received in revised form 24 March 2017; Accepted 10 April 2017
Available online 13 April 2017
0928-0987/ 

of HbA1c is slow, which makes it necessary to perform longer-term clinical trials to assess treatment effects adequately at steady-state. Thus it would be of value to have a method to obtain the longitudinal translation of glucose levels from a short trial to HbA1c levels at end of treatment in a long trial. Furthermore, a translation of glucose to HbA1c values within the same trial could be useful. Such a translation needs to account for factors affecting variability in steady-state MPG-HbA1c ratio. These include: RBC life-span, which is influenced by age, effects on glucose transport into RBCs (e.g. by insulin therapy), and factors affecting the glucose-independent component of HbA1c (Lledó-García et al., 2013).

The relationship between plasma glucose and HbA1c has previously been described using both empirical methods and semi-mechanistic models. In particular, the relationship between HbA1c and plasma glucose at steady state has been established through linear regression models in many studies (Rohlfing et al., 2002; Liang et al., 2010; Nathan et al., 2008; Ladyzynski et al., 2014). Several mathematical models have also been developed, based on physiological mechanisms such as glycosylation and life span of erythrocytes (Mortensen et al., 1984; Lledó-García et al., 2013; Kjellsson et al., 2013; Ladyzynski et al., 2014). Such models are often developed in order to understand and/or describe the underlying biological processes behind the observed data. A number of other quantitative models describing the relationship between plasma glucose and HbA1c (Møller et al., 2013; Hamrén et al., 2008; Landersdorfer and Jusko, 2008) have been developed based on clinical trial data. These models, like the regression methods, offer a framework for prediction of HbA1c based on clinical trial data.

Although some models (regression and semi-mechanistic) have been developed using large populations of subjects, they have generally not been assessed and compared across different trials and types of treatments, except in the case of the model proposed by Møller et al. (2013). This is an indirect response model which has been shown to accurately predict HbA1c at end-of-trial based on early glucose and HbA1c data from the trial. Therefore, this model can be used as a tool for optimization of late-stage clinical drug development within diabetes. However, in order to be able to use the model across different populations, it is important to know how the relationship between MPG and HbA1c varies across populations. To this end we have made an analysis of covariate effects using a large database of 8927 subjects in the context of the longitudinal model proposed by Møller et al. (2013). The covariates we have analysed are: age group, BMI, gender, race, diabetes duration, and pre-trial treatment. To our knowledge, no attempt has previously been made to analyse the impact of covariates on the glucose-HbA1c relationship in the context of a longitudinal model. Several studies have analysed the impact of covariates using regression methods, and it has been shown that even though HbA1c values vary little over time within the same individual, they vary considerably between individuals (Yudkin et al., 1990; Meigs et al., 1996). In particular, effects of race on the relationship between HbA1c and glucose have been described. Differences in HbA1c levels between races have been recognized for many years, but it has previously been attributed to differences in access to medical care and quality of treatment (Herman and Cohen, 2012). However, the significantly higher HbA1c values in some race groups are now mostly considered to be explained by true biological variation, in factors such as haemoglobin glycosylation or red blood cell survival. While the existence of a race effect is widely recognized, the effects of other covariates are more debated.

## 2. Materials and methods

In this study we used data from 16 late-phase clinical trials (phase III/IV) in subjects with type 2 diabetes (see Tables 1 or 2 for ClinicalTrials.gov identifiers) with a total of 8927 subjects to study the impact of covariates on the relationship between MPG and HbA1c. The selected trials included treatment arms with oral antidiabetic drugs; GLP-1 analogues; various insulin treatments including basal insulins and basal/bolus insulin combinations; as well as combinations of these treatments. All trials were conducted in accordance with the ethical principles in the Declaration of Helsinki and approved by the participating institution's ethics committees.

The trials were required to have a duration of 6 months or longer and to include 24 h glucose profiles (such as 7–10 point self-measured plasma glucose profiles, for study details see Table 2) as well as HbA1c sampling at least three times during these 26 weeks. Only trials with HbA1c sampling at baseline were included, and MPG values were calculated as the weighted averages from the glucose profiles using $AUC_{0-24\ h}/24$ h. The subjects included in the trials were type 2 diabetes patients, and only completers of the trials were included in the analysis set. Demographics and baseline characteristics for the subjects included in the analysis are summarised by trial in Tables 1 and 2, respectively.

Using a longitudinal model, covariates were analysed on the intercept in the MPG-HbA1c steady-state relationship. In brief, the model was an indirect response model for HbA1c with a first order elimination rate constant $k_{out}$ and a formation rate given by $k_{in} * (MPG + \beta)$ (Møller et al., 2013). At steady state, the MPG-HbA1c relationship in this model is given by $HbA1c = (k_{in} / k_{out}) * (MPG + \beta)$, i.e. a linear relationship with a slope given by $k_{in}/k_{out}$ and an intercept given by $\beta * k_{in} / k_{out}$. The values of $k_{in}$ and $k_{out}$ were fixed to 0.081%/(week * mmol/L) and 0.226 $week^{-1}$, respectively, based on the original publication (Møller et al., 2013). All other model parameters were re-estimated and the results are available in the Supplemental material. Because $k_{in}$ and $k_{out}$ were fixed, covariates were only analysed on the intercept parameter β. This is equivalent to investigating covariate effects on the intercept in the linear relationship between steady-state MPG and steady-state HbA1c. Covariates could also affect the slope in this relationship, but this would correspond to changes in glycosylation dynamics, which was not the focus of the current study. A more detailed description of the model is published elsewhere (Møller et al., 2013).

The covariate model was developed using a full model approach with inclusion of all covariates in one step (Hu et al., 2011). The NONMEM software (version 7.1.2, ICON Development Solutions, Ellicott City, MD) (Beal et al., 2009) with first-order conditional estimation (FOCE) was used. Analysed covariates included age group, BMI (continuous), gender, race, diabetes duration (continuous), and pre-trial treatment, and the covariate effects were estimated on an additive scale, meaning that each effect can be interpreted directly as a change in HbA1c at steady state for a given MPG. Differences between trials were taken into account by also estimating an effect for each trial. To avoid convergence issues in the subsequent likelihood profiling, the trial effects in the final model were fixed to their estimated values, and the covariate effects were re-estimated. This did not change the point estimates for any of the covariate effects. Goodness-of-fit plots for the final model are available in the Supplemental material. Four sensitivity analyses were conducted: one with no trial effects; one with additional terms for interaction between the pre-trial treatment and diabetes duration effects; and two univariate sensitivity analyses with no pre-trial treatment effects and no diabetes duration effects, respectively. The results of the sensitivity analyses are available in the Supplemental material.

Using the point estimates from the longitudinal model and 95% confidence intervals determined based on likelihood profiling, a forest plot showing changes in HbA1c at steady state for a given MPG was created to visualize the association with the investigated covariates. The results from the pharmacometric analysis were also checked using steady-state regression analysis for each covariate in turn. In these regression analyses, a common slope was estimated, and only the intercept was allowed to differ between covariate categories. For the continuous covariates; diabetes duration and BMI, the data was divided into groups for the regression analysis. For diabetes duration, the data was divided into 3 groups; below 2 years, between 2 and 20 years and