

DIABETES MELLITUS

A method to predict the metabolic effects of changes in insulin treatment in subgroups of a large population based patient cohort

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Abstract. This case-control study was designed to analyse predictors of the effects on HbA1c levels in 4001 type 1 and type 2 diabetic patients after changing their insulin treatment. Patients from 15 outpatient diabetic clinics were treated with basal insulin and multiple injections of short-acting insulin. The effects on HbA1c of changing from NPH insulin to insulin glargine as basal insulin were studied, compared to patients continuing with NPH insulin. The following possible predictors were examined with multiple regression analysis: age, sex, type and duration of diabetes, smoking, metformin use, insulin requirement, number of basal doses per day, BMI and HbA1c at baseline. The difference between the two regression functions yielded the effect of switching treatment to insulin glargine compared to

continuing with NPH insulin. Male gender, low BMI and high baseline HbA1c levels were significant predictors for a greater decrease in HbA1c when changing to insulin glargine. For example, for men with a BMI of 25 and an HbA1c of 8.0%, there was a calculated mean benefit in HbA1c of 0.26 percentage points by changing to insulin glargine, whereas women with a BMI 30 had no benefit of such a change. Thus, changing to insulin glargine had best effect in male patients with low BMI. This is one of the first studies designed to find responders to insulin treatment. Analyses of predictors may prove useful in order to tailor insulin treatment in diabetic patients in clinical practice. The clinical effects need to be confirmed in other studies and randomised controlled trials.

Key words: Diabetes mellitus, Glargine, HbA1c, Insulin, NPH, Prediction, Regression to the mean

Introduction

Optimal glycaemic control is one of the keystones in modern diabetes care [1, 2]. In type 1 diabetes, as well as in many type 2 diabetic patients, this is best achieved through individually tailored use of different kinds of insulin in order to meet the individual's physiological needs [3]. When a certain course of therapy is considered, the decision is often based on the mean effect of a particular agent, as demonstrated by clinical trials. However, the effects of any treatment will vary between different individuals and there is an urgent need of studies of responders and non-responders to insulin treatment [4].

The two most commonly used basal insulins today are insulin glargine and NPH (Neutral protamine Hagedorn) insulin. Insulin glargine is a basal insulin with a duration of action of 20–24 h and a flatter effect curve than NPH insulin [5, 6]. Several studies have evaluated the mean effect on HbA1c of insulin glargine compared with NPH insulin, but the results have been contradictory [7–19]. To the best of our knowledge, no studies have addressed any concept to

study responders and non-responders for insulin glargine or any other types of insulins. Thus, the aim of this retrospective study, based on computerised medical records of 4001 type 1 and type 2 diabetic patients, was to ascertain whether there are factors that can predict the effects on HbA1c after changing from NPH insulin to insulin glargine.

Methods

Patients

In this study, which was approved by the Ethics Committee of Göteborg University, 1,639 subjects and 2,362 control patients from 15 outpatient diabetes clinics were included. Data were collected from January 1998 until May 2004 via a medical record system (Journalia AB, Sweden) [20, 21] related to 12,948 patients who made in total 178,785 visits.

We aimed at including all patients that had changed their basal insulin treatment from NPH insulin to insulin glargine during treatment with multiple daily

Table 1. Baseline characteristics*

	Patients changing to insulin glargine	Control patients
Number of patients	1639	2362
Age (years)	46.2 ± 15	52.2 ± 15
Women (%)	44%	49%
HbA1c (%)	7.49 ± 1.6%	7.16 ± 1.4%
Body mass index (kg/m ²)	25.5 ± 4.2	26.7 ± 4.5
Weight (kg)	75.9 ± 14.7	80.9 ± 14.9
Insulin dose (U/kg/day)	0.64 ± 0.25	0.70 ± 0.28
Number of basal doses	1.4 ± 0.5	1.4 ± 0.5
Basal insulin, proportion (%)	44.6 ± 14.0%	45.4 ± 12.9
Insulin injections (n/day)	4.1 ± 0.8	4.1 ± 0.6
Type 1 diabetes, proportion (%)	85%	69%
Diabetes duration (years)	19 (IQR 11–29)	21 (IQR 13–29)
Duration of insulin (years)	18 (IQR 10–29)	18 (IQR 9–27)
Meal-time insulin, proportion (%)		
Insulin aspart	37%	19%
Insulin lispro	56%	43%
Regular insulin	7%	38%
Oral antidiabetic drugs, proportion (%)		
Metformin	21%	11%
Sulfonylurea	4%	0%
Thiazolidinediones	2%	0%

Values are presented as means ± SD unless stated otherwise.

insulin injections (MDI). It was also necessary that at least one HbA1c value existed before and a certain period of time after the change to insulin glargine to be able to evaluate any change in HbA1c. The rationale for this approach was to include as many patients as possible, which is important in a prediction analysis. When comparing mean effects of two groups an alternative is to match the groups but in this case this would have led to a large amount of excluded patients, a less representative population and the final effect would only have been less power. Inclusion criteria for the group treated with insulin glargine were: (1) current treatment with insulin glargine, (2) previous treatment with NPH insulin with MDI, and (3) HbA1c values available before treatment with insulin glargine and at least 60 days after the start of treatment with insulin glargine. For the selection of a representative control group continuing treatment with NPH insulin with MDI, the following inclusion criteria were chosen: (1) the last HbA1c value measured within the past 12 months, and (2) at least one additional HbA1c value within 200 days of the last value. Values of HbA1c were examined before baseline, at baseline and repeatedly after the change to treatment with insulin glargine. We also studied how the change affected insulin dose, the number of daily insulin injections, the proportion of basal insulin, and body weight.

The following patient characteristics were studied: age, sex, duration of diabetes, type of diabetes, smoking, metformin use, insulin requirement (units of insulin per kg body weight, U/kg), number of basal

doses per day, BMI and HbA1c at baseline. Diabetes clinics in Sweden use HbA1c methods regularly calibrated to the HPLC Mono-S method. The HbA1c values can be converted to the DCCT standard levels using the formula [22]: HbA1c (DCCT) = 0.923 × HbA1c (Mono-S) + 1.345. The median duration of the interval between patient visits to the clinic was 3.9 months (interquartile range (IQR) 2.5–5.4). The median duration of therapy for the group treated with insulin glargine was 10 months (IQR 6–15), and for the control group 12 months (IQR 9–15). The mean date of the last visit was February 2004.

Statistical analysis

When searching for predictors of glycaemic effects of insulin glargine we used multiple regression analysis and the same technique was applied to the control group. For the group changing to glargine as well as for the control group, we used the significant predictors to create a multiple regression model to predict the effect on the HbA1c level. The difference between the two regression functions yielded the effect of switching treatment compared to continuing with the NPH insulin.

The values presented are given as the means ± standard deviation (SD). HbA1c values and reported findings prior to and after treatment were compared using paired *t*-tests. Several values were obtained from most patients. The difference between the baseline and the last HbA1c value did not show a normal distribution. Therefore, the transformation $Z^{-1}(F(x))$ was applied, where Z^{-1} is the inverse of the

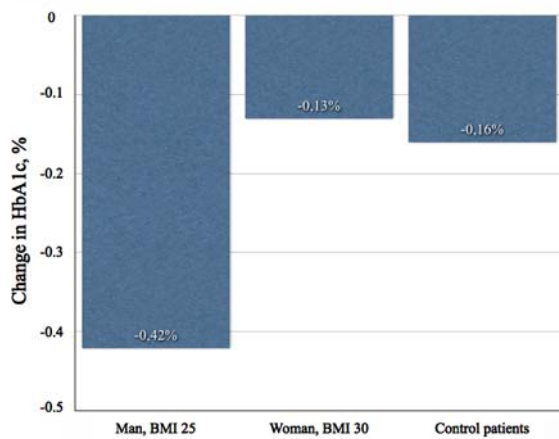


Figure 1. Predicted effects of changing to insulin glargine as basal insulin. Examples calculated from the regression models. Men with low BMI are predicted to show a decrease in HbA1c more than three times greater than that in women with BMI 30 when changing from NPH insulin to insulin glargine. Women with a BMI 30 showed no better effect than the control subjects. The values shown are for patients with a baseline HbA1c of 8.0%.

standardised normal distribution function, and $F(x)$ is the empirical distribution function of the difference. The function $Z^{-1}(F(x))$ was approximated by piecewise linear and continuous functions. The transformed difference had an almost perfect normal distribution. Different transformations were used for the group treated with insulin glargine and for the control group.

Multiple regression analysis was performed with the transformed differences as the dependent variable. Using a stepwise procedure we studied the independent variables age, sex, duration of diabetes, type of diabetes, smoking, use of metformin, insulin requirement, number of basal doses, BMI and

HbA1c at baseline. From the results of the multiple regression analysis we calculated the conditional frequency functions of the original difference given the values of the independent variables. Using the frequency functions it was then possible to determine the expected values of the original difference, depending on the variables included in the multiple regression analysis. The regression coefficients for gender in the two groups were compared with a test based on the normal distribution.

Results

Baseline characteristics for the group treated with insulin glargine and the control group are given in Table 1. The groups were not meant to be matched due to the premises. When examining possible predictors of an effect on glycaemic control after changing treatment to insulin glargine, we found that sex (in favour of men, $p < 0.001$), low BMI ($p < 0.01$) and high baseline HbA1c ($p < 0.001$) significantly lowered the HbA1c value (Figure 1). In the control group, statistical significance was only obtained for HbA1c at baseline ($p < 0.001$). For the group treated with insulin glargine the multiple correlation coefficient was 0.51 and the standard deviation around the regression function 0.770. In the control group the correlation coefficient was -0.38 and the standard deviation 0.858.

Since we found BMI, gender and HbA1c at baseline to be predictors of a better effect of the change in treatment to insulin glargine, we constructed a model to predict the effect of this change based on these factors (Table 2). The following variables were found not to be statistically significant and were thus omitted from the model: age, type of diabetes, duration of diabetes, smoking, use of metformin, number of basal doses per day, and insulin

Table 2. Predicted change in HbA1c (%) after changing from NPH insulin to insulin glargine in relation to baseline BMI, gender and HbA1c

	Patients changing to insulin glargine				Control group
	Women		Men		
Baseline HbA1c level	BMI 25 kg/m ²	BMI 30 kg/m ²	BMI 25 kg/m ²	BMI 30 kg/m ²	
HbA1c 5%	0.765	0.834	0.554	0.623	0.625
HbA1c 6%	0.444	0.512	0.232	0.301	0.358
HbA1c 7%	0.121	0.19	-0.092	-0.022	0.1
HbA1c 8%	-0.204	-0.134	-0.42	-0.349	-0.157
HbA1c 9%	-0.535	-0.463	-0.76	-0.686	-0.42
HbA1c 10%	-0.881	-0.805	-1.125	-1.044	-0.699
HbA1c 11%	-1.261	-1.176	-1.542	-1.447	
HbA1c 12%	-1.704	-1.602	-2.047	-1.93	
HbA1c 13%	-2.249	-2.122	-2.684	-2.535	
HbA1c 14%	-2.939	-2.778	-3.487	-3.3	

The control group shows the effect of regression to the mean since the controls with high HbA1c decrease in HbA1c although there was no change in therapy.

requirement at baseline. When compared with the control group (NPH insulin with MDI), gender had a significantly greater influence as a predictor of change in HbA1c ($p = 0.0053$).

HbA1c decreased by an average of 0.18% after changing from NPH insulin to insulin glargine ($7.49 \pm \text{SD}1.6$ vs. $7.31 \pm 1.3\%$, $p < 0.001$). After the change the insulin consumption increased from 0.64 ± 0.25 to 0.65 ± 0.25 U/kg body weight/day ($p < 0.01$), the number of daily basal insulin injections decreased from 1.4 ± 0.5 to 1.1 ± 0.3 ($p < 0.001$), the proportion of basal insulin increased from $44.6 \pm 14\%$ to $47.0 \pm 13\%$ ($p < 0.001$), and body weight increased from 75.9 ± 14.7 to 76.4 ± 14.9 kg ($p < 0.001$). In the control group HbA1c increased on average by 0.05% (from $7.16 \pm 1.4\%$ to $7.21 \pm 1.4\%$, $p < 0.05$). There was no significant difference between mean HbA1c values at the time of changing to insulin glargine and two years before the change ($7.49 \pm 1.6\%$ vs. $7.48 \pm 1.6\%$). The mean number of HbA1c measurements prior to the change of treatment was 3.4 ± 1.5 .

Discussion

This study shows that it is possible to analyse what patient groups have benefited most of a treatment since it has been introduced in routine care by use of multiple regression models. In this study male gender, low BMI and high HbA1c levels predicted a greater decrease in HbA1c when switching from NPH insulin to insulin glargine during MDI therapy. A statistical model was constructed including BMI, gender and HbA1c at baseline, which predicted the change in HbA1c, when changing from NPH insulin to insulin glargine, better than an average change. For the control group remaining on NPH insulin, only HbA1c at baseline was a statistically significant predictor. A model depending on this variable predicted the HbA1c change better than the average change in this group of patients.

To the best of our knowledge, no other studies have been published on the prediction of the glycaemic effects of insulin glargine or other types of basal insulin. The question of whether specific patient groups benefit more from insulin glargine or NPH insulin is of great importance, not least since earlier comparative studies of these types of insulin have shown conflicting results.

When changing from insulin glargine to NPH insulin the prediction model shows, for example, that in a man with a BMI of 25 and baseline HbA1c of 8.0% the HbA1c would decrease by 0.42%, whereas a woman with a BMI of 30 and the same baseline HbA1c value would show a decrease of 0.13% (Figure 1, Table 2). The control subjects with the same baseline HbA1c (8.0%) showed a decrease of 0.16%, although there was no change in therapy (regression to the mean). Thus,

for a man with a BMI 25 and baseline HbA1c of 8.0% whose HbA1c decreased by 0.42% after changing to glargine, the effect associated with the change in treatment in comparison to continuing with NPH, is $0.42 - 0.16 = 0.26\%$, and for a woman with a BMI 30 it is $0.13 - 0.16\% = -0.03\%$ (i.e., no effect). This example demonstrates the combined influence of BMI and gender, but also the regression to the mean effect. Thus, the regression model gives a better prediction of the effect on HbA1c change than an average estimate. Different values of the predictors could be inserted into the prediction equations to estimate the change in HbA1c after changing to insulin glargine in comparison with remaining on NPH insulin, thereby giving an even better prediction of the mean effects on HbA1c (Table 2).

There is often a risk of selection bias in retrospective studies. When changing from NPH insulin to insulin glargine, the prediction model accounted for age, sex, duration of diabetes, type of diabetes, smoking, metformin use, insulin need (units of insulin per kg), body weight, number of basal doses per day, BMI and HbA1c at baseline. Thus, all these factors were corrected for in developing the prediction model. The control group differed mainly by having better glycaemic control and fewer type 1 diabetic patients (Table 1). However, the same factors were corrected for in the control group as in the glargine group and, hence, no selection bias concerning these factors is likely to have influenced the comparisons between the groups. Selection bias could still have occurred if any other variable was important for insulin effect. One factor of interest, for example, is hypoglycaemic episodes. Several studies have reported fewer hypoglycaemias in patients treated with insulin glargine than NPH insulin [7, 9, 15, 17]. Thus, insulin sensitive men on treatment with NPH insulin may e.g. possibly suffer from more hypoglycaemic episodes than women, and therefore overeat, which might cause a difference in effects of the different insulin regimens. Unfortunately, it is difficult to objectivize data on the frequency and severity of hypoglycaemic episodes as well as self-monitored blood glucose measurements in clinical practice, and such data were not included in the calculations. The occurrence of diabetic complications as a marker of severity of disease would also have been of interest to include in the model to adjust for potential confounding by indication [23]. However, we included the duration of diabetes and level of HbA1c at baseline which are both known to be associated with diabetic complications [24–28]. Other potential factors of interest to incorporate in the model would be the time available for insulin treatment in the daily routine, knowledge of diabetes, motivation and mental state, but these are difficult to measure and record even in a clinical trial.

One can only speculate about any explanation why lean men have benefited most of receiving insulin

glargine at these 15 outpatient hospital clinics in Sweden. Previous reports on other types of insulin state that a low BMI is associated with a lowering of the HbA1c [29]. However, as far as we know, the change in HbA1c due to gender has not been reported earlier. The finding that men decreased more in HbA1c than women after changing to insulin glargine was highly significant in the multiple regression analysis. It is not yet known what causes this difference. Psychological factors are not likely, as no influence of sex was seen in the control group using NPH insulin. Furthermore, there was no difference in HbA1c levels between men and women before changing their insulin treatment. A great number of patients are needed to detect such a phenomenon and so far, pharmacokinetic studies on insulin glargine have included few subjects, mostly men [5, 6]. One hypothesis is that the observed difference is a sex-related variation in the pharmacokinetics of insulin, since oestrogen has been shown to affect subcutaneous tissue insulin clearance in women [30]. Speculating in a non-pharmacological explanation, the observed sex-related difference could be related to the starting up of a new therapy, e.g. that care givers for some reason could have been worse at titrating insulin doses in women or that women have had less time in their daily living to take care of the titrations of their new treatment. Ideally, prospective trials should be conducted in order to specifically examine the factors with a potential to influence the glycaemic effects of insulin treatment, such as gender, weight, hypoglycaemia, blood glucose determinations as well as dietary habits and physical activity. Such studies may prove important to assist the physicians in their decision to change the treatment of diabetic patients in clinical practice.

The results of large observational studies are important to establish the effects of medical treatments in clinical practice but also for the design of randomised trials with respect to size and inclusion criteria. From our results we estimated that 2×123 male patients with a BMI ≤ 28 and HbA1c $> 8.0\%$ would be needed to achieve the power 80% when comparing a control group with a group changing from NPH insulin to insulin glargine. It is assumed that the test is two-sided at the level of $p = 0.05$. The calculated mean difference was 0.33 percentage points. If no special selection is performed, the expected difference is 0.10 percentage points and the number of patients required to achieve the power 80% is 2×1410 . It would thus be of great value to analyse the results of the previously published randomised trials together in a prediction meta-analysis in an attempt to gain better knowledge of the effects of insulin glargine on glycaemic control.

Our prediction model was based on a pair of regression functions. One for the group changing from NPH insulin to insulin glargine during MDI

and one for the group continuing with NPH insulin during MDI. The assumptions behind these regression functions could be investigated in several ways. One issue was the distribution of the change of HbA1c. We rejected the simple assumption about normal distribution and performed the mathematically most suitable transformations in order to achieve normally distributed variables. Another issue of validation was the regression functions, which could be studied by goodness of fit tests (e.g. χ^2 test or a special F -test). However, the acceptance of the H_0 -hypothesis does not say so much about potential improvements that could be achieved. If the model is made more complex (extended with more parameters), there is a risk that the model is overfitted, which means that random characteristics are included in the model. So our validation was restricted to the question about normal distribution.

In summary, the key aspect of this study was to introduce the concept of prediction of the effects of different pharmacological treatments, in particular with insulin preparations. Analyses of predictors may prove useful in order to tailor insulin treatment in diabetic patients in clinical practice. In this large population based patient cohort lean men decreased most in HbA1c when changing from NPH insulin to insulin glargine during MDI treatment. It is important to acknowledge that other factors than the type of insulin can have contributed to this finding. The reason is that there are risks of selection bias as well as confounding by indication when evaluating pharmacological agents in non-randomised settings. The result should thus be subject for further generation of hypotheses and should be confirmed in future studies. Randomised controlled trials are also needed before clinical recommendations can be made.

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