Predictors of Glycemic Response and Change in HbA1c Following Newly Initiated Basal Insulin Among Insulin Naïve Adults With Type 2 Diabetes

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Abstract- This sub-analysis of the Iran-AFECT study was to determine the baseline characteristics are predicting the likelihood of attainment of HbA1c goal and changing in HbA1c after initiation of basal insulin glargine in insulin naïve people with type 2 diabetes not adequately controlled with oral glucose-lowering drugs. Iran-AFECT was a 24-week, prospective, multicenter, observational study of people with type 2 diabetes initiated or switched to insulin glargine. In this sub-analysis, we included all insulin naïve people. Glycemic response was defined as HbA1c≤7.0% and/or change in HbA1c at week 24. Data on 433 participants were included. The mean HbA1c was 8.9%±0.9% at baseline which decreased to 7.6%±1.2% (P<0.001). By week 24, 36% of the participants reached HbA1c≤7.0%. In univariate analysis, the strongest association was for the baseline HbA1c (r^2=0.32, P<0.001). In multivariate analysis, predictors of change in HbA1c were baseline HbA1c (r^2=0.29, *P<0.001*), and dosing of glargine (r^2=0.01, P=0.02). The baseline HbA1c was accounting for 88% of explainable variances in HbA1c. The best cut-off predicting glycemic response for baseline HbA1c was 8.5%. Among factors predicting response to initiating basal insulin therapy with insulin glargine, baseline HbA1c is the strongest predictor explaining most of the variances in HbA1c change.

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Introduction

In people with type 2 diabetes, good glycemic control can delay the development and progression of long-term diabetes-related complications (1-3). When lifestyle modification and the combination of oral pharmacological therapies could not restore glycemic control, adding a single injection of a basal insulin is recommended (4,5).

Insulin analogs have been shown to improve glycemic control when added to oral glucose lowering drugs (OGLDs) in insulin naïve people (6-8). Although some patients can achieve the HbA1c target of ≤7.0% by adding basal insulin to prior oral therapies, others may still exhibit little improvement in glycemic control despite insulin therapy. Recent recommendation considering personalized management of hyperglycemia in people with type 2 diabetes can be helpful in achieving glucose targets (9,10).

A few studies explored factors associated with good glycemic control in people with type 2 diabetes. (11-16). However, these are mostly retrospective, in the setting of clinical trials, or included various insulin regimens. Understanding the baseline characteristics that predict good glycemic response after adding a basal insulin analog in routine clinical practice setting might better guide clinical decision making for this form of insulin therapy.

Thus, the aim of the present analysis was to explore the potential predictors of success in achieving good glycemic control in people with poorly controlled type 2 diabetes on combination of oral glucose lowering drugs, when adding a single basal injection of insulin glargine in routine clinical care setting.

Materials and Methods

Iran-AFECT study was a multicenter, prospective, observational study to explore the efficacy and safety of basal insulin glargine in people with type 2 diabetes not

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adequately controlled (7.0%<HbA1c≤10.0%) by oral lowering drugs and/or NPH as basal insulin. The physicians took the independent decision to initiate or switch insulin glargine as a part of routine clinical care. HbA1c was assessed at enrollment, after 12 weeks of insulin initiation, and by the end of the study (week 24). The primary objective was to measure the percentage of patients achieving HbA1c≤7.0% at the end of the study. Safety measures included symptomatic hypoglycemia, nocturnal hypoglycemia, and adverse drug reactions (ADRs).

For the current study, data of the insulin naïve subjects who completed the 24 weeks of insulin therapy were analyzed. These included insulin naïve participants who had finished the study. Response to insulin was defined as:

1. HbA1c≤7.0% at week 24
2. Change from baseline in HbA1c at week 24

Demographic and clinical lists of baseline predictors of interest analyzed in predictor analysis were: age, gender, Body Mass Index (BMI) , diabetes duration, blood pressure, lipid profile, FBG, HbA1c, diabetes related complications, OGLDs, and dose of insulin glargine at initiation. Reported measures at the end of the study which used for explanatory analysis include serum triglyceride (TG), Total cholesterol, Low-density lipoprotein (LDL), High-density lipoprotein (HDL), Fasting Blood Glucose (FBG), and dose of insulin glargine at week 24. The relationship between baseline HbA1c and the frequency of reaching the HbA1c target were also explored.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS version 18.0, Chicago IL). Means±SD or frequency (proportions) was used for descriptive statistics. Kolmogorov-Smirnov test and histogram were used to test normality assumption, and if the distribution was skewed, nonparametric tests such as Mann Whitney U test were used. A *t*-test was performed to compare two independent normal groups. Chi square test was used to determine whether there is a significant difference in the proportion of two categories. Associations, univariate and multivariate analysis were the results of logistic and linear regressions. Odds ratios and 95% CIs, unstandardized coefficient and Coefficient of determination (R2) were reported, if applicable. P<0.05 were considered as statistically significant.

Results

Of total Iran AFECT study population (723), 433 insulin naïve patients were included in this study. The mean HbA1c was 8.9%±0.9% at baseline, which decreased to 7.6%±1.2% (P<0.001) by week 24. The mean reduction in HbA1c from baseline was -1.4%±1.2%.

Mean HbA1c at insulin initiation was 8.5% among those who reached to HbA1c≤7.0% compared with 9.1% in non-responders. Table 1 shows the relationship between baseline characteristics and the likelihood of reaching the HbA1c target. In logistic regression analysis, the odds for HbA1c was 0.54 (0.41-0.69), P<0.001. The odds for the other baseline parameters were statistically non-significant (Table 2).

We then examined the association of baseline factors with change in HbA1c level by week 24 in a univariate analysis. Among various baseline factors, serum triglyceride, total cholesterol, LDL, fasting plasma glucose, HbA1c, and the presence of peripheral neuropathy showed good predictive power and were statistically significant (r^2>0.01, P<0.05). The strongest association was for the baseline HbA1c level (r^2=0.32, P<0.001). In a multivariate analysis, predictors of HbA1c change were baseline HbA1c (r^2=0.29, P<0.001), and glargine dose (r^2=0.01, P=0.02) (Table 3).

Furthermore, the categorical ranges of baseline HbA1c were used to explore the relationship between baseline HbA1c and reaching to HbA1c target by the end of the study. Around one fourth of patients reached to HbA1c target by the end of the study. On the other hand, 63% of those with baseline HbA1c<8% achieved the target. The mean change in HbA1c was more with higher baseline HbA1c level (Figure1).

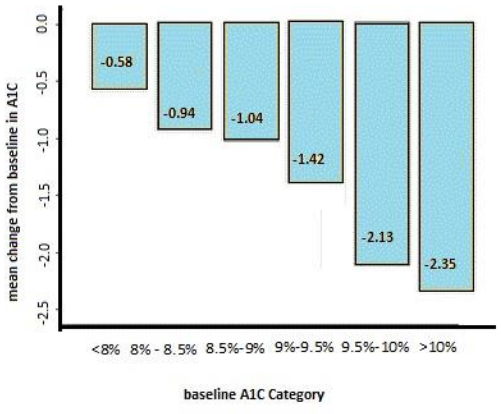

Figure 1. Mean change from baseline, after 24 weeks of treatment, stratified by baseline HbA1c

Table 4 shows the results of the explanatory analysis of the end of study measurements associated with

HbA1c change by week 24. In the univariate analysis, serum TG, FBG, and glargine dose showed statistically significant association. However, in multivariate analysis, FBG and glargine dose remained with good predictive power ($r^2 \geq 0.01$).

To determine a threshold for baseline HbA1c level in diabetic people who reach to HbA1c≤7.0% at 24 weeks, a graph was plotted, looking at the relationship between proportions versus baseline HbA1c levels. A decreasing response to basal insulin glargine could be seen, as the baseline HbA1c level increased.

We then determine the best cut-off for the baseline HbA1c that predicts responsiveness to basal insulin glargine, using ROC curve analysis. The analysis revealed a cut-off point of 8.5% for the baseline HbA1c. This cut off had a sensitivity of 78% and specificity of 54% for attaint of HbA1c≤7.0%, AUC:0.67; (0.61,0.72).

Table 1. Relationship between baseline characteristics and HbA1c by week 24

	HbA1C≤7.0% (visit3) N=157 (36%)	HbA1C>7.0% (visit3) N=276 (64%)	*P*
Gender (Female)	99 (63%)	167 (61%)	0.61
Age (yr)	53.79±11.55	55.24±10.89	0.21
BMI (kg/m^2)	28.09±4.43	27.91±5.13	0.71
Diabetes duration (yr)	9.54±6.85	8.74±5.97	0.43
SBP (mmHg)	127.88±16.69	132.60±18.97	0.01
DBP (mmHg)	79.30±9.23	81.00±8.63	0.04
TG (mg/dl)	186.85±86.19	188.17±96.32	0.94
HDL (mg/dl)	44.38±12.47	42.66±11.46	0.28
LDL (mg/dl)	103.93±32.29	107.79±35.74	0.27
Chol (mg/dl)	186.99±39.94	190.54±45.85	0.42
FBG (mg/dl)	194.32±54.84	213.54±65.51	0.001
HbA1C (%)	8.52±0.99	9.07±0.85	<0.001
Nephropathy (+)	14 (9%)	30 (11%)	0.56
Neuropathy (+)	33 (22%)	83 (31%)	0.051
Retinopathy (+)	16 (11%)	32 (13%)	0.66
Sulphonylurea use at baseline (yes vs. no)	119 (76%)	216 (78%)	0.56
Glargine daily dose (unit/day)	14.75±7.74	16.40±8.18	0.007

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DSP: Diastolic Blood Pressure; TG: Triglyceride; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; Chol: Total Cholesterol; FBG: Fasting Blood Glucose; HbA1c: Glycosylated hemoglobin

Table 2. Association between baseline characteristic and HbA1c attainment

	Odds ratio	CI for odds ratio	*P*
SBP	0.99	(0.97 1.00)	0.07
DBP	0.99	(0.96 1.02)	0.60
FBG	0.99	(0.99 1.00)	0.53
HbA1C	0.54	(0.41 0.69)	<0.001
Glargine dose	0.97	(0.94 1.02)	0.06
Neuropathy	0.82	(0.49 1.36)	0.44

SBP: Systolic Blood Pressure
DSP: Diastolic Blood Pressure
FBG: Fasting Blood Glucose
HbA1c: Glycosylated hemoglobin

Table 3. Univariate and multivariate analysis of baseline factors used for prediction analysis

	Univariate analysis		
	B±SE	**R^2**	***P***
Gender (female)	-0.001±0.001	0.001	0.63
Age	-0.003±0.006	0.001	0.59
BMI	0.004±0.013	0.000	0.77
Diabetes duration	0.002±0.010	0.000	0.81
SBP	0.003±0.003	0.002	0.36
DBP	0.004±0.007	0.001	0.58
TG	-0.001±0.001	0.01	0.04
HDL	0.000±0.005	0.000	0.98
LDL	-0.004±0.002	0.01	0.047
Chol	-0.003±0.001	0.014	0.015
FBG	-0.003±0.001	0.023	0.002
HbA1C	-0.74 ±0.05	0.32	<0.001
Nephropathy	-0.18±0.20	0.002	0.36
Neuropathy	-0.44±0.13	0.03	0.001
Retinopathy	-0.23±0.19	0.004	0.22
Metformin daily dose	0.000±0.00	0.001	0.54
Glargine daily dose	0.014±0.007	0.009	0.053
	Multivariate analysis		
	B±SE	**Partial R^2**	***P***
TG	0.00±0.001	0.001	0.45
LDL	0.002±0.002	0.002	0.39
Chol	-0.003±0.002	0.004	0.21
FBG	0.001±0.001	0.002	0.44
HbA1c	-0.74±0.06	0.29	<0.001
Neuropathy	-0.013±0.12	<0.001	0.92
Glargine daily dose	0.01±0.007	0.01	0.02

✷Model $R^2 = 0.33$

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DSP: Diastolic Blood Pressure; TG: Triglyceride; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; Chol: Total Cholesterol; FBG: Fasting Blood Glucose; HbA1c: Glycosylated hemoglobin

Table 4. Univariate and multivariate explanatory analysis for HbA1c change

	Univariable analysis		
	B±SE	**R^2**	***P***
TG	0.001±0.001	0.08	0.09
HDL	-0.002±0.003	0.03	0.50
LDL	0.002±0.001	0.07	0.16
Chol	0.002±0.002	0.06	0.19
FBG	0.012±0.001	0.36	<0.001
Glargine daily	0.022±0.006	0.17	<0.001
	Multivariable analysis		
	B±SE	***P***	
TG	0.001±0.001	0.47	
FBG	0.01±0.002	<0.001	
Glargine dose	0.014±0.006	0.015	

TG: Triglyceride; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; Chol: Total Cholesterol; FBG: Fasting Blood Glucose

Discussion

Initiation of basal insulin is recommended in people with type 2 diabetes, who cannot meet glycemic targets on metformin and life style modification±OGLD (4).

In this analysis of 433 insulin naïve people not adequately controlled by metformin±glibenclamide in routine clinical practice, 36% attained of glycemic targets by initiating basal insulin glargine by completion of the study.

Previous studies explored the factors that might predict attainment of glycemic targets by initiating insulin treatment in people with type 2 diabetes. However, the criteria for glycemic response were different, the population was diverse, and various types of insulin regimens were examined (11-14,17).

We explored various demographic and clinical variables to identify predictive factors associated with glycemic response to basal insulin initiation.

Lower HbA1c at baseline was the best predictor: OR=0.54, *P*=0.00 for 1% difference. As the strongest prediction factor, it was accounting for 88% of the explainable variance in HbA1c. Other demographic or clinical factors such as glargine dose, the presence of peripheral neuropathy, lipid parameters, and fasting blood glucose revealed some predictive power in the univariate analysis. However, in the multivariate analysis, baseline HbA1c, and glargine dose at initiation had acceptable predictive power, although the predictive power for the insulin dose was markedly reduced (r2=0.01, *P*=0.02).

At the end of the study, serum triglyceride, fasting blood glucose, and glargine dose had some explanatory power in the univariate analysis. Again, the power dropped out in the multivariate analysis, although fasting blood glucose and the glargine dose remained to have low explanatory power.

We have also found that participants with higher baseline HbA1c experienced greater decline by the end of the study. Several previous observations showed similar results (18-22). On the other hand, those with higher baseline HbA1c levels were less likely to reach HbA1c target≤7.0%. Less than one-third of the participants with baseline HbA1c>8.5% reached the target.

The INSTIGATE (The INSulin TItration-GAining an understanding of the burden of Type 2 diabetes in Europe) demonstrated that baseline HbA1c is the major determinant of change in HbA1c (23). Moreover, Home *et al*., recently reported the predictors of glycemic response of people with type 2 diabetes initiating insulin therapy in the A1chieve study (24). The major determinant of change in HbA1c was the baseline HbA1c level (12). Similar to the finding of the present study, other demographic and clinical factors did not have good predictive power.

In our study, we did not find any association between diabetes duration and glycemic response. This was in line with Nichols *et al*., (16) and contradictory to Benoit *et al*., (14). One can argue that longer duration of diabetes might be associated with disease severity; however, insulin use could improve glycemic status independent of diabetes duration. More importantly, age and body weight were not predictors of change in HbA1c.

Owen (11) reported that older age was more responsive to insulin therapy, while the predictive power of age was low in the analysis of the A1chieve study (12). In contrast to these findings, Nichols *et al*., found that younger age was a predictor of good glycemic control. Controversies exist for the other possible predictor's such age and body weight as well. The observed differences in the predictors of glycemic response might be due to differences in patient populations, ethnicity, clinical practice patterns, and mixture of different interventions or insulins.

The strength of our study was the use of single basal insulin analog in a group of insulin naïve people not adequately controlled on OGLDs for the considerable duration in routine clinical practice. We also considered various demographic and clinical factors in uni and multivariate analyses.

There were also some limitations. We could not measure patient adherence to study protocol because of the nature of the observational study. The titration protocol was based on the decision of the physicians. We could not also take into account the role of comorbid conditions objectively.

In summary, we found that baseline HbA1c is a powerful predictor of glycemic response and change in HbA1c in people with type 2 diabetes initiating basal insulin glargine in the routine clinical practice setting. We have also shown that although the majority of people with more poorly controlled diabetes could not reach to the HbA1c target of ≤7.0%, significant changes could be observed with a single basal insulin analog. This is very important issues considering the concept of individualized therapy targets for glycemic control, especially in older people with diabetes.

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