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Twice-daily insulin glargine for patients with uncontrolled type 2 diabetes mellitus.

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Insulin glargine is recombinant human insulin analog that is commonly used in patients with type 2 diabetes as well as those with type 1 diabetes. Pharmacokinetic and pharmacodynamics studies of insulin glargine had shown that it has an onset of action that ranged from 1.2 to 1.8 h while its duration of action is 18 to 26 h [1]. Because of its long duration of action insulin glargine is usually prescribed once daily. However, several reports have shown that the administration of insulin glargine once daily is not enough to achieve adequate glucose control in some patients requiring a twice daily dosing [2–9]. The first report on using insulin glargine twice daily was published shortly after its availability [2]. It described a patient with type 1diabetes who had consistently elevated bedtime glucose values on once daily insulin glargine administered in the evening. There was significant improvement in glucose values after changing the frequency of insulin glargine to twice daily as a split dose every 12 h. Albright and colleagues found that twice daily glargine therapy was required in patients with type 1 diabetes who developed morning hypoglycemia and/or afternoon hyperglycemia while on once daily therapy [3]; the twice daily regimen was associated with a significant reduction in HbA_{1c} levels compared to patients who were on once daily therapy.

Objectives

We aimed to examine changes in glucose control in a cohort of patients with type 2 diabetes after switching from once daily to twice daily insulin glargine U-100 due to uncontrolled glucose levels. The reason for switching from once to twice daily insulin glargine therapy was the limited ability to titrate insulin glargine doses at bedtime because of morning hypoglycemia (early morning or before breakfast) and/or persistent hyperglycemia before dinner despite titrating meal insulin doses at lunch.

Methods

Patients were required to be on basal/meal insulin regimen for at least 6 months to be enrolled. We also investigated potential specific characteristics that can predict the need for twice daily administration of insulin glargine. The study protocol was approved by Hamad medical corporation institutional review board. Data on patient characteristics including demographics, duration of diabetes, weight, body mass index, doses of insulin glargine and meal insulin, and use of non-insulin glucose-lowering medications were collected while on once daily and after the switch to twice daily glargine therapy. Secondary analysis evaluated the potential predictors for the use of twice daily insulin glargine including body weight, body mass index, duration of diabetes, HbA_{1c} levels, insulin glargine dose and meal insulin dose. This was undertaken by comparing the twice daily glargine group to a matched cohort of 210 patients with type 2 diabetes who were on basal/meal insulin regimen that included once daily insulin glargine administered at bedtime. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 22. Descriptive and inferential statistics were used to characterize the study sample and test hypotheses. Paired sample *t*-test was used to assess the primary objective of the study which was to identify a difference in HbA_{1c} levels when insulin glargine is switched from once daily to twice daily. Bi-variate analysis was performed using independent sample *t*-test or Mann Whitney *U* test whenever appropriate to compare quantitative variables between those who were on insulin glargine once daily to those who were on twice daily therapy. Qualitative variables between the two groups were compared using Pearson Chi-square test or Fisher exact test as appropriate. Multiple logistic regression model was used to identify significant independent factors associated with the use of twice daily insulin glargine therapy after adjusting for potentially confounding factors. The Wald test was computed on each predictor to determine which were significant. Adjusted odds ratio and 95% confidence interval for the adjusted odds ratio were reported. A "P" value < 0.05 (two tailed) was considered statistically significant.

Results

A total number of 50 patients on twice daily insulin glargine were included. Men formed 58% of the cohort; mean age was 55.3 ± 8.2 years; mean duration of diabetes was 17.6 ± 8.2 years; mean body mass index was 32.8 ± 5.5; mean follow up period was 8.2 ± 2.1 months. Mean HbA_{1c} decreased significantly from 10.3 ± 1.5% (89.1 ± 8.5 mmol/mol) while on once daily insulin glargine to 8.4 ± 1.3% (68.3 ± 8.3 mmol/mol) on twice daily therapy, $P < 0.001$. Mean daily insulin glargine dose increased from 53 ± 20.9 units to 77.8 ± 29.4 units while on once and twice daily glargine therapy respectively, $P < 0.001$. Conversion from once to

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Table 1
Changes in clinical parameters on switching from once-daily to twice-daily insulin glargine therapy.

Factors	Group (n = 50)		P-Value
	On once-daily Glargine	On twice-daily Glargine	
Weight (kg)	87.4 ± 15.9	89.4 ± 16.2	0.002
Glargine dose (units/day)	53 ± 20.9	77.8 ± 29.4	< 0.001
Meal insulin dose (units/day)	38.7 ± 38.6	59.2 ± 50.2	< 0.001
HbA_{1C} % [mmol/mol]	10.3 ± 1.5 [89.1 ± 8.5]	8.4 ± 1.3 [68.3 ± 8.3]	< 0.001

*Results are expressed as mean ± standard deviation.

twice daily dosing resulted in a significant increase in the mean total daily insulin dose from 91.7 ± 45.5 to 138.3 ± 69.9 units, P < 0.01. Table 1 shows the changes in several parameters when patients were switched from once to twice daily insulin glargine therapy. There was no change in the use of other glucose-lowering medications or their doses after the switch to twice daily glargine therapy. In the secondary analysis using multivariate logistic regression revealed that HbA_{1c} level (adjusted odds ratio 1.65, 95% CI 1.3–2.0, P < 0.01) and insulin glargine dose (adjusted odds ratio 1.35, 95% CI 1.2–1.5, P < 0.001) were independent predictors of twice daily therapy.

Discussion

This study demonstrated that the use of twice daily insulin glargine U-100 in patients with uncontrolled type 2 diabetes on basal/meal regimen significantly improved glucose control. The main reason that limited the titration of insulin doses when these patients were on once daily glargine is the occurrence of morning hypoglycemia and/or persistent hyperglycemia before dinner despite titrating meal insulin doses at lunch. Data on the use of twice daily glargine therapy is limited and involved mainly patients with type 1 diabetes [2–9]. The largest study that examined this issue involved 82 patients with type 1 diabetes [3]; the protocol recommended changing the dosing of insulin glargine to twice daily if HbA_{1c} levels remained high and/or if glucose levels were persistently high before dinner despite titration of the dose of meal insulin at lunch. The investigators found that 24% of patients required the use of glargine twice daily which resulted in a significant improvement in HbA_{1c} levels. Improvement in glucose profile was demonstrated in other reports that included smaller number of patients with type 1 diabetes [4–6]. These results were not replicated in two other studies: Garg and colleagues found no difference in glucose control and the incidence of hypoglycemia in a cohort of 104 patients with type 1 diabetes on twice daily insulin glargine compared to 161 patients on once daily glargine [7]. Burge et al found no difference in serum insulin and glucose levels in 10 patients with type 1 diabetes after the administration of equivalent daily doses of insulin glargine injected once or twice daily during a 38-hour fast [8]. We found only one published study on the use of twice daily insulin glargine in patients with type 2 diabetes [9]. In this study, the investigators evaluated 18 patients with type 2 diabetes who were on twice daily insulin glargine and compared them to 117 patients on once daily therapy. The authors reported improvement in glucose control in patients on twice daily therapy and found that the dose of glargine was the main predictor for switching to twice daily regimen. Our findings, with a larger number of patients, represent the second study of twice daily insulin glargine therapy in patients with type 2 diabetes and confirm the efficacy of this regimen.

In conclusion, twice daily insulin glargine results in a significant improvement in glucose control in selected patients with type 2 diabetes. We suggest to consider this regimen for patients who continue to have uncontrolled glucose on basal/meal insulin regimen particularly if they are on high doses of insulin glargine. Prospective randomized controlled trials should help confirm these findings and define patient groups who will benefit from twice daily insulin glargine therapy.

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