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The Characteristics of Patients whose both Fasting and Postprandial Glucose were Controlled by Once Daily Basal Insulin Monotherapy

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Abstract

Background: Several meta-analyses compared insulin monotherapy and combined therapy of insulin and oral hypoglycemic agents (OHA). However, these were not consistent and not focused to individualization. Therefore, we try to elucidate the characteristics of patients whose both fasting and postprandial glucose were controlled by once daily basal insulin monotherapy.

Methods: The data of this study are part of our previous study which investigated characteristics of responders on different medications for controlling postprandial glucose levels after optimizing fasting glucose levels by insulin glargine. Background OHA cessation for 2 weeks of initial washout period and then insulin glargine was initiated. Oral glucose tolerance tests after initial wash out period and 7 point self-monitoring blood glucose test for 3 days at each step was completed by each subject.

Results: The patients in Controlled group were younger, had a lower baseline A1c, and lower OGTT 2hr PPG levels than patients in the Non-Controlled group. Controlled group showed higher homeostasis model analysis % β (HOMA %B), corrected insulin response (CIR) and insulin-to-glucose ratio (IGR) than Non-Controlled group. Homeostasis model analysis insulin resistance (HOMA IR), 1/fasting insulin (by FI) and insulin sensitivity index (ISI) were similar between the two groups.

Conclusions: In our study, some patients can be well controlled both fasting and postprandial glucose level with once daily insulin glargine monotherapy. Patients able to do so were younger, had lower baseline HbA1c, lower oral glucose tolerance test (OGTT) 2h PPG and higher makers of insulin secretion.

Keywords: Type 2 diabetes; Basal insulin monotherapy; FPG; PPG

Introduction

The concept of pathophysiology of type 2 diabetes changed from simply insulin resistance to ominous octet [1]. Treatment guidelines of type 2 diabetes suggested a patient centered approach, emphasizing individualization by patient to patient [2,3]. Since type 2 diabetes mellitus is a progressive disease due to more and more attenuating pancreatic beta cell function [4,5], more and more patients need insulin therapy over time since diabetes diagnosis [3]. So, clinicians must consider many things prior to making a decision for specific treatment regimens for patients with diabetes, including insulin regimens.

The consistent 24-h action profile of synthetic basal insulin offers reliability, predictability and lower risk of hypoglycemia, which is one of biggest barrier in insulin treatment [6]. We can easily and reliably predict insulin effect with fasting glucose and titrate insulin dose without hypoglycemia. Those have made the initiation of insulin use easier, and the rate of insulin use for type 2 diabetes has been steadily increasing. Initiating basal insulin is a simple and effective method to control fasting glucose, but there is still a need for a consensus on how best to control postprandial glucose except for the addition of ultra-short acting insulin injections in patients on basal insulin therapy. That's why we started our previous original study [7]. But, through this study, we found that some patients could control postprandial glucose, as well as fasting plasma glucose, with once daily basal insulin.

Several meta-analyses compared insulin monotherapy and combination therapy of insulin and OHA [8-11]. Their results were not consistent and focused on glycemic control represented by HbA1c. They were not interested in individual patients, so did not investigate the clinical predictors for PPG control with once daily insulin monotherapy. Therefore, we attempted to elucidate the characteristics of patients whose both fasting and postprandial glucose were controlled by once daily basal insulin monotherapy.

Methods

This methodology is part of our previous study [7]. The original study was a multi-center, crossover, open labeled prospective clinical trial (Clinical trial reg. no. NCT 00437918). All participants gave written informed consent before participating in the study. The protocol was in accordance with the Helsinki Declaration, approved by the local ethics committee and registered as a clinical trial in www.ClinicalTrials.gov.

The enrollment criteria was men and women, aged 40-80 years, with type 2 diabetes with inadequate glycemic control (HbA1c ≥ 7.5% and ≤ 10%) while taking oral agents and insulin naïve. After 2 weeks of initial washout period, insulin glargine was initiated as a monotherapy with once daily injection. After fasting glucose level was optimized (less than 120 mg/dL) by basal insulin dose titration within 2 weeks, patients

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with mean postprandial glucose over 180 mg/dL preceded onto the next step. Their results are reported in Figure 1 [7]. We herein analyzed the characteristics of patients not included in the original study because their PPG was lower than 180mg/dL with basal insulin monotherapy. We divided patients into 2 groups as controlled PPG with insulin glargine only (group Controlled) and non-controlled PPG with insulin glargine only (group Non-Controlled).

After an overnight fast, the participants had a standard 75-g oral glucose tolerance test (OGTT) at the end of the screening period. Venous samples for the measurement of plasma glucose and serum insulin concentrations were taken before glucose ingestion and at 30 and 120 minutes after glucose load. Glucose was analyzed using the hexokinase/G6P-DH technique (Boehringer Mannheim, Mannheim, Germany), and insulin was analyzed with human insulin ELISA kit (Linco research, MO, USA). Seven-point self-monitored blood glucose (SMBG) was obtained at 3 preprandial glucose levels measured before each meal, 3 postprandial glucose levels measured 2 h after the beginning of each meal and bedtime glucose level for 3 days at the end of each study period. SMBG was performed using the same BG meter provided by the investigator (Optium Xceed, Abbott). Physicians, with the aid of qualified dietitians, educated all of the patients on the standard diet and exercise therapy for the duration of the study, and were requested to maintain this throughout the study periods, while ensuring they perform the SMBG correctly. Hypoglycemia was classified as mild (confirmed ≤ 60 mg/dl) or severe (show the blood glucose levels, requiring third-party assistance). We measured glucose excursions, such as mean glucose level, standard deviation (SD), mean average glucose excursion (MAGE) [12] or average daily risk range (ADRR) [13]. We analyzed baseline markers of insulin resistance and beta cell function. Homeostasis model assessment of insulin sensitivity (HOMA-IR) and Homa % B were calculated [14]. Insulin secretion was also estimated by two methods, 1) the corrected insulin response (CIR) = (100 x 30-min insulin)/(30-min glucose x [30-min glucose – 70 mg/dL]) and 2) the insulin-to-glucose ratio (IGR) = (30-min insulin – fasting insulin)/(30-min glucose – fasting glucose). Insulin sensitivity was also calculated by two methods, 1) 1/fasting insulin and 2) the insulin sensitivity index (ISI), which is 22.5/(fasting insulin x [fasting glucose/18.01]).

Statistical methods

The clinical characteristics were presented as frequencies and percentages for categorical variables and as means ± SD for continuous variables. Continuous variables were compared using t-test or Wilcoxon rank sum test after normality check and the categorical variables were analyzed using Chi-square test.

Results

Baseline clinical and laboratory characteristics according to control with basal insulin monotherapy

Among the 88-screened subjects, two were excluded because they showed too high glucose levels (HbA1c>10%, FBS>250) and hyperglycemic symptoms during screening period. Nine dropped out of the study after the initial screening period. Insulin glargine monotherapy could not decrease fasting glucose to target level (<120 mg/dL) in four patients. 73 patients finally completed screening. Among them, 15 patients showed well controlled fasting and postprandial glucose with once daily basal insulin only. We divided them to controlled PPG with insulin glargine only (group Controlled). 58 patients proceeded onto the next step in original study (Figure 1) and divided to non-controlled PPG with insulin glargine only (group Non-Controlled) in this study. The age of group Controlled was significantly low than group Non-Controlled (51.8 ± 5.03 vs. 58.3 ± 9.78 years old, p=0.003). BMI of both groups were 25.9 ± 3.37 and 25.2 ± 7.19 kg/m^2, respectively (Table 1). The duration of diabetes in both groups were 8.2 ± 5.3 and 9.9 ± 6.9 years. The mean HbA1c levels and OGTT 2h PPG of group Controlled was significantly low than group Non-Controlled, 7.63 ± 0.25 %, 221.8 ± 17.9 mg/dL and 8.54 ± 0.21%, 248.8 ± 44.7 mg/dL, respectively. The daily doses of insulin glargine in group Controlled and Non-Controlled were 0.28 ± 0.15 IU/kg and 0.36 + 0.26 IU/kg, respectively. The levels of total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol did not show significant differences between the two groups.

Mean glucose levels by 7 point SMBG and glucose variability

Insulin glargine treatment lowered self-monitored before-breakfast (BB) glucose levels to target. Patients in group Controlled showed significantly low postprandial glucose levels of after-breakfast (AB), after-lunch (AL) and after-dinner (AD) compared with patients in group Non-Controlled (Figure 2). Group Controlled also had lower premeal glucose levels at before-lunch (BL), before-dinner (BD) and before-sleep (HS) compared with group Non-Controlled. We compared the markers of glucose excursions between the two groups. Mean glucose standard deviation (SD), mean amplitude glucose excursion (MAGE) and average daily risk range (ADRR) were significantly lower in Controlled group than Non-Controlled group (Figure 2).

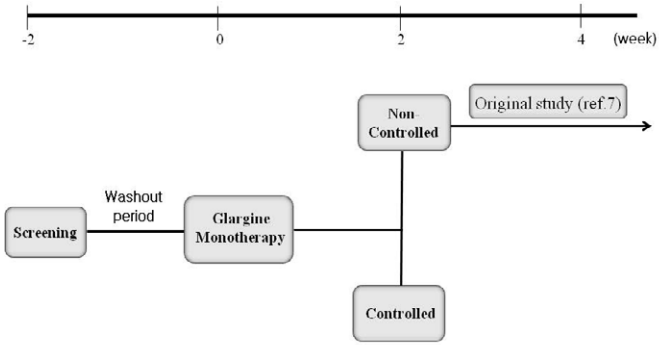

Figure 1: Treatment schedule and patient disposition during the study.
OGTT: Oral Glucose Tolerance Test; SMBG: Self-monitoring of Blood Sugar

	Controlled	Non-Controlled	p value
Number (%)	15/73 (20.5%)	58/73 (79.5%)	
Age (years)	51.8 ± 5.03	58.3 ± 9.78	0.003*
BMI (kg/m^2)	25.9 ± 3.37	25.2 ± 7.19	0.623
DM duration (years)	8.2 ± 5.3	9.9 ± 6.9	0.411
Daily glargine dose (IU/Kg)	0.28 ± 0.15	0.37 ± 0.22	0.155
Baseline HbA1c (%)	7.63 ± 0.25	8.54 ± 0.21	0.01*
OGTT 2h PPG (mg/dL)	221.8 ± 17.9	248.8 ± 44.7	0.04*
Total cholesterol (mg/dL)	169.6 ± 35.7	163.7 ± 35.5	0.601
Triglyceride (mg/dL)	142.8 ± 32.7	147.8 ± 14.7	0.879
HDL cholesterol (mg/dL)	53.9 ± 2.9	48.9 ± 1.88	0.197
LDL cholesterol (mg/dL)	90.1 ± 8.6	90.4 ± 4.4	0.978

Table 1: Baseline characteristics of subjects.
Data was shown by mean ± S.D.
BMI; body mass index,
Controlled: controlled both FPG and PPG by once-daily insulin glargine only,
Non-Controlled: within target FPG, but not controlled PPG by once-daily insulin glargine only
*p<0.05 by independent T-test

The markers of insulin secretion and sensitivity of two groups

We calculated the markers of insulin secretion and insulin sensitivity. HOMA %Beta was higher in Controlled group compared to Non-Controlled group (Figure 3A). Corrected insulin response (CIR) and insulin to glucose ratio (IGR) also showed significant differences between Conrolled and Non-Controlled groups (Figure 3B and C). HOMA IR, insulin sensitivity index (ISI) and 1/fasting insulin (1/FI) did not show any differences between groups divided by controlled PPG with insulin glargine only (Figure 4 D-F).

Hypoglycemia and adverse events

There were no episodes of severe hypoglycemia in the two groups. The proportion of participants experiencing mild hypoglycemic episodes was 8% in the Non-Controlled group and 0% in the Controlled group. Since hypoglycemia in the Non-Controlled group was related to medications in the original study, there was no hypoglycemia related insulin glargine monotherapy. No other serious treatment related adverse events were recorded. There were a total of 15 adverse events reported in the Non-Controlled group related to nateglinide and acarbose treatment in the original study, and they were mostly mild abdominal flatulence and dyspepsia, and in general well tolerated. There are no other adverse events reported with once daily insulin glargine monotherapy.

Discussion

We herein try to elucidate the characteristics of patients whose both fasting and postprandial glucose (FPG and PPG, respectively) were controlled by once daily basal insulin monotherapy. Our results showed 20.5% patients were able to control both FPG and PPG with once daily insulin glargine monotherapy. The patients in Controlled group, whose PPG was controlled with once daily insulin glargine monotherapy, was younger, had lower baseline A1c and lower OGTT 2hr PPG levels than patients in the Non-Controlled group, whose PPG was not controlled with once daily insulin glargine monotherapy. Controlled group showed higher markers of insulin secretion and glucose excursion than the Non-Controlled group. The markers of insulin sensitivity were similar between the two groups.

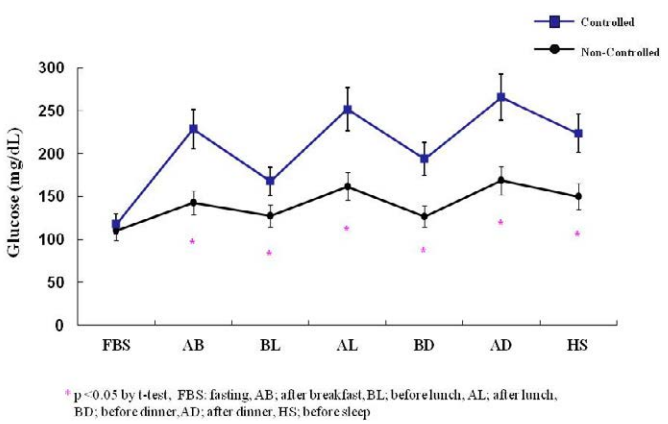

Figure 2: Mean glucose levels measured by 7 points between Controlled and Non-Controlled groups. Controlled: controlled both FPG and PPG by once-daily insulin glargine only, Non-Controlled: controlled FPG, but not controlled PPG by once-daily insulin glargine only.
FBS: Fasting, AB: After Breakfast; BL: Before Lunch; AL: After Lunch; BD: Before Dinner; AD: After Dinner and HS; bedtime
*p<0.05 by t-test

When we initiate insulin treatments for patients that fail oral hypoglycaemic agents (OHA), there are two different options: changing to insulin therapy alone or adding insulin to OHA. Several previous reviews comparing insulin monotherapy to combination therapy of insulin / oral hypoglycaemic agents (OHA) showed inconsistent results. One of them recommended not to use combination therapy in insulin-treated type 2 diabetes because the improvement in glycemic control was only slight and blood glucose concentrations could not be near normal [10]. Other reviews suggested combination therapy was more appropriate and a suitable option to insulin monotherapy in type 2 diabetes using insulin, according to their analysis [9,11]. Another meta-analysis reported that insulin monotherapy and combination therapy of insulin with OHA provided similar glycemic control [8]. However, these meta-analyses mentioned that the studies were not

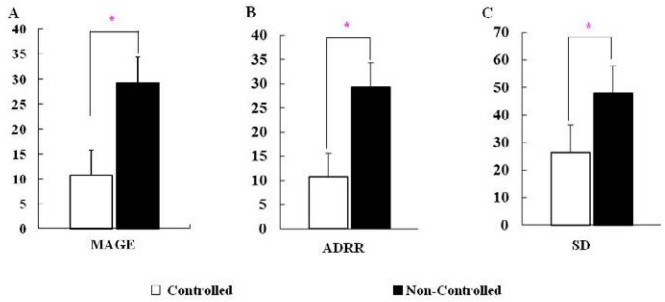

Figure 3: The comparison of glucose excursions between controlled and Non-Controlled groups. Controlled: controlled both FPG and PPG by once-daily insulin glargine only, Non-Controlled: controlled FPG, but unable to control PPG by once-daily insulin glargine only.
*p<0.05 by t-test
MAGE: Mean Average Glucose Excursion; ADRR: Average Daily Risk Range; SD: Standard Deviation

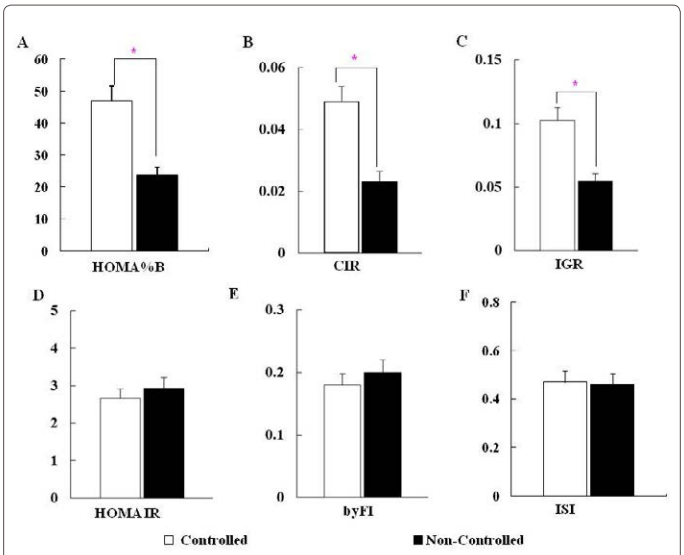

Figure 4: The comparison of markers of insulin secretion (Homa %B, CIR, IGR) and insulin sensitivity (Homa IR, ISI and 1/FI) between Controlled and Non-Controlled groups. Controlled: controlled both FPG and PPG by once-daily insulin glargine only, Non-Controlled: controlled FPG, but unable to control PPG by once-daily insulin glargine only. HOMA%β; Homeostasis Model Analysis %β, CIR; corrected insulin response, IGR; the insulin-to-glucose ratio, HOMA IR; Homeostasis Model Analysis Insulin Resistance, 1/FI; 1/fasting insulin, ISI; insulin sensitivity index
*p<0.05 by t-test

well designed and the kind of insulin was almost always intermediate insulin, not basal insulin. They did not focus on postprandial glucose (PPG) or clinical predictors of more suitable for insulin monotherapy. Previous studies did not consider individualization of insulin treatment. Therefore, they could not extrapolate who would be able to control PPG, as well as FPG, with just once daily insulin monotherapy.

Our study showed the percentage of patients who controlled PPG with basal insulin only was 20.5%. Compared to a sub-analysis of Koreans in a large observational study, the percentage of patients taking concomitant OAD with basal insulin was 83.79% [15]. That result may represent about 17% of patients taking basal insulin and who do not take any OAD in real practice. The reasons of the relative higher percentage in our study may be due to the small number of subjects, study design and the short study period.

Patients who controlled PPG with basal insulin monotherpy were younger, had lower baseline A1c and lower OGTT 2hour PPG levels compared to patients who were unable to control PPG. A recent paper confirming the predictive factors of insulin analog user in 28 different countries reported that a higher baseline A1c was the most powerful predictor for lower final A1c [16], but sub-analysis of Korean patients showed better response in patients who had lower A1c [15]. Our study was conducted to stop all background OHA and initiate and adjust insulin dosage to reach an optimal FPG goal, which differs from studies that added insulin as a background OHA. Our study showed that patients with good makers of insulin secretion could control both FPG and PPG with once daily insulin glargine only. Since their FPG and PPG were within the target levels, their markers of glucose excursion were better than the Non-Controlled group. Duration of diabetes and daily insulin glargine dosage were also lower in Controlled group compared to Non-Controlled group, but not reach statistical significance. The ORIGIN study [17], which is an example of early insulin treatment, showed that people receiving insulin glargine typically required fewer additional antidiabetic agents at the end of the study than those receiving standard care. Although we cannot find similar studies designed like ours, several studies showed that people with lower HbA1c levels at baseline, lower body mass index (BMI) and shorter duration of T2DM were more likely to achieve glycaemic targets [18-20].

There are several limitations in our study. Our study subjects' number was too small because it was a prospective design for a specific purpose. This result was not a prespecified outcome. We did not perform multiple regression analysis for predictors due to the small number of subjects and the study duration was short. However, our results may have one clinical implication, which is that individualization in diabetes management is important in insulin regimen.

In conclusions, some patients can be well controlled through both fasting and postprandial glucose levels with once daily insulin glargine monotherapy. Further investigation is needed for more comprehensive individual patient-centered approach in type 2 diabetes management.

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