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Comparative efficacy of exenatide versus insulin glargine on glycemic control in type 2 diabetes mellitus patients inadequately treated with metformin monotherapy

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ABSTRACT

Purpose: Comparative efficacy of exenatide versus insulin glargine primarily on glucemic control, and secondarily on body mass index (BMI), lipid profile and blood pressure, in type 2 diabetes mellitus (T2DM) patients suboptimally treated with metformin monotherapy.

Material/Methods: Forty-seven inadequately treated T2DM patients on metformin assigned to exenatide (n=18) or insulin glargine (n=29) for 26 weeks. Glycosylated hemoglobin (HbA1c), serum lipids, BMI, systolic and diastolic blood pressure, and adverse events, including episodes of hypoglycemia and gastrointestinal symptoms, were recorded.

Results: Either treatment had a similar favorable mean reduction in HbA1c. However, more patients in exenatide group achieved HbA1c $\leq$ 7% at the 26th week compared with insulin glargine group (p=0.036). Insulin glargine group had significantly more episodes of hypoglycemia compared with exenatide group (p=0.039). Gastrointestinal adverse events were non-significantly higher in the exenatide group. A significantly greater BMI reduction was observed in exenatide group, whereas BMI was not altered in insulin glargine group. Total and LDL cholesterol (p=0.012), and triglycerides (p=0.016) significantly decreased, whereas HDL cholesterol increased (p=0.021) in the exenatide group, whereas only total cholesterol decreased in insulin glargine group. Changes in systolic and diastolic blood pressure were insignificant in both groups.

Conclusions: Exenatide provided similar reduction in HbA1c, but fewer episodes of hypoglycemia, compared with insulin glargine. Exenatide had also a favorable effect on weight loss, although more gastrointestinal adverse events. Exenatide may provide a justified alternative in second line treatment of T2DM, but more trials are required to elucidate its long-term safety and cost-effectiveness.

Key words: Diabetes mellitus type 2, exenatide, glucagon-like peptide-1, hemoglobin A glycosylated, insulin glargine

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by progressively declining β-cell function in the presence of insulin resistance [1]. The prevalence of T2DM is increasing rapidly in both developed and developing countries. The emerging pandemic occurs due to the combined effects of population ageing, rising levels of obesity and inactivity, and greater longevity [2].

T2DM is associated with significant morbidity and mortality; therefore, its management is of paramount importance. Most clinical practice guidelines recommend metformin as the first-line oral anti-hyperglycemic drug in most patients with T2DM, when glycemic control cannot be achieved by lifestyle interventions [3-5]. However, second-line therapy, when glycemic control is inadequate with metformin monotherapy, often lacks specific recommendations [6]. This is further implicated by the increase in the number of available

agents for T2DM, including glucagon-like peptide-1 (GLP-1) analogues and basal insulin analogues, either of which has been proposed as second-line treatment [3-5].

Exenatide is a GLP-1 analogue having 53% homology with human GLP-1. By binding to GLP- 1 receptors, exenatide increases the glucose-mediated insulin secretion from β-cells, suppresses glucagon secretion, slows gastric emptying and increases satiety. Exenatide has been rarely involved in hypoglycemia and has been associated with weight loss, but may cause gastrointestinal adverse events, such as nausea, vomiting diarrhea and, rarely, acute pancreatitis [7].

Insulin glargine is a long acting analogue that can mimic the action of endogenous basal insulin. The once daily dosing scheme is easy to use and adhere, especially for those requiring assistance to inject insulin. Insulin glargine is associated with reduced episodes of hypoglycemia, especially nocturnal. However, it has been linked to weight gain, possibly due to reduction of glucosuria [8].

In a recent meta-analysis, either basal insulin analogues or GLP-1 analogues had a similar effect on glycosylated hemoglobin (HbA1c), but only GLP-1 analogues had a weight reducing effect, when added on metformin monotherapy [6]. Furthermore, basal insulin, but not exenatide, increased the episodes of hypoglycemia. However, there are currently limited head-to-head studies for the comparative efficacy and safety between these two treatment strategies [9-13]. The main aim of this study was the evaluation of comparative efficacy of exenatide versus insulin glargine on glycemic control in T2DM patients inadequately treated with metformin monotherapy, thereby the main end-point being HbA1c change. Secondary end-points were the change in BMI, systolic and diastolic blood pressure, lipid profile, as well as comparative safety, mainly episodes of hypoglycemia, gastrointestinal adverse events and serious adverse events.

MATERIALS AND METHODS

This was a single-center, 26-week, prospective, open label, non-randomized trial. The study's protocol was approved by the local ethics committee and was in accordance with the declaration of Helsinki. All patients provided an informed consent at the screening visit. Patients with T2DM on metformin monotherapy (1700 to 2000 mg daily) and inadequate glycemic control were added either exenatide or insulin glargine. Randomization was not performed, because we intended to simulate real-world clinical practice. Patients assigned to exenatide started with 5μg twice daily for one month and, subsequently, were shifted to 10 μg twice daily up to the end of the study. Patients assigned to insulin glargine started with initial dose of 10 IU once daily at bedtime and were instructed to titrate according to Initiate Insulin by Aggressive Titration and Education (INITIATE) [14]. In brief, titration was based on self-monitoring blood glucose levels (SMBG) targeting to fasting glucose ≤100 mg/dl. When fasting SMBG was ≥ 100 mg/dl the insulin dose was increased by 2 units, until fasting SMBG was between 81 and 100 mg/dl. No change was made in metformin dose or any hypolipidemic or any anti-hypertensive treatment in any participant throughout the study period.

Inclusion criteria were: 1) age 45-75 years; 2) HbA1c >7%; and 3) monotherapy with metformin at a stable dose for at least two months before baseline assessment. Exclusion criteria were 1) age<45 or >75 years; 2) type I diabetes mellitus; 3) history or current treatment with any other antidiabetic drug, including sulfonylurea, meglitinide, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, GLP-1 agonist and acarbose, or insulin; 4) renal failure; 5) anemia of any cause; 6) history of any malignancy; 7) current pregnancy; 8) addiction to any drug. Major criterion to assign selected patients to exenatide was BMI > 35 kg/m^2; however, other parameters were also secondarily considered, including duration of T2DM, consequences of potential episodes of hypoglycemia and individual financial situation.

Anthropometric measurements and physical examination was performed and fasting blood samples were obtained between 8:00 and 9:00 a.m. at baseline and at 26th week (± 2 weeks). Systolic and diastolic blood pressure were recorded and BMI was calculated by the formula: body weight [kg] / height^2 [m^2]. Serum total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol and glucose were measured within 1 hour after blood drawing, with standard methods using an automated analyzer (Olympus AU2700; Olympus, Hamburg, Germany). HbA1c was also measured within 1 hour with latex immunoagglutination inhibition assay using an automated analyzer (DCA 2000, Bayer Diagnostics, Leverkusen, Germany; precision coefficient of variation 3.4-4.4%). Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula [15].

Episodes of hypoglycemia (frequency and severity), any gastrointestinal adverse event, including nausea, vomiting, diarrhea and abdominal pain, and any serious adverse event, were recorded throughout the study. For this purpose, the patients were given a contact telephone number and were advised to get in contact with study's investigators soon after experiencing any hypoglycemia (SMBG<60 mg/dl), gastrointestinal or other adverse event. An episode of hypoglycemia was considered major, if the patient had SMBG<60 mg/dl and simultaneously needed help of another person, because of severe impairment in consciousness or behavior, or if the episode resulted in loss of consciousness or seizure that was promptly reversed upon administration of glucose.

Statistical analysis

Data for continuous variables are presented as mean ± standard deviation (SD). Data for categorical variables are presented as numbers and/or percentages. Kolmogorov-

Smirnov test was used to test the normality of distribution of continuous variables. Independent-samples T-test or Mann-Whitney test was used for between group comparisons. Paired-samples T-test or Wilcoxon Signed Ranks test was used for within group comparisons. Adjustment for age and BMI was performed by multivariate analysis of covariance. Chi-Square test was used for comparisons of categorical variables. Statistical analysis was performed by SPSS for Windows version 17.0 (SPSS Inc., Illinois, USA). Significance was set at $p<0.05$ for all the above tests. *Post-hoc* power analysis was performed by G*Power software (University of Heinrich-Heine, Dusseldorf, Germany).

RESULTS

Baseline and 26-week data of both groups are presented in *Table 1*. A significant within group HbA1c reduction in either exenatide (p=0.006) or insulin glargine group (p=0.010) was observed at 26th month. There was not significant between group difference in HbA1c in numerical terms *(Tab. 1)*. Notably, between group difference in HbA1c remained similar after adjustment for age and BMI. Similarly, there was not statistically significant difference in the decrease of HbA1c at 26th week (-1.3 ± 0.5% in exenatide vs. -0.5 ± 0.2% in isulin glargine group; p=0.131). However, 9 (50%) patients of exenatide versus 6 (21%) of insulin glargine group achieved HbA1c ≤ 7% at the 26th week (p=0.036).

Six patients experienced hypoglycemia (one episode for each) in insulin glargine group, whereas none in exenatide group (p=0.039). However, no patient experienced major hypoglycemia. One patient experienced gastrointestinal complication (nausea) in insulin glargine group, whereas three (all nausea) in exenatide group (p=0.114). Nausea was self-limited in all cases. No serious adverse event was observed. Notably, all reported complications were self-limited and no patient discontinued the study.

Patients on exenatide had significant within group BMI reduction (p=0.004), due to weight loss, whereas insulin glargine group had no essential change in BMI *(Tab. 1)*. Total cholesterol was similarly reduced within groups (p=0.010 in exenatide and p=0.014 in insulin glargine group). However, LDL cholesterol (p=0.012) and triglycerides (p=0.016) were significantly decreased, and HDL cholesterol significantly increased (p=0.021) only within exenatide group. Systolic and diastolic blood pressure was essentially unchanged within both groups. There were no between group differences regarding either lipid profile or blood pressure at 26th month *(Tab. 1)*.

To partly override the baseline between group difference in BMI and triglycerides *(Tab. 1)*, we performed between group comparisons of deltas (Δ; change between 26th month and baseline) in continuous variables. Δ(BMI) (-2.5 ± 1.8 vs. 0.1 ± 1.4; p<0.001) and Δ(triglycerides) (-37 ± 16 vs. -10 ± 14; p=0.022) were significantly lower in exenatide compared to insulin glargine group. There was no other between group Δ difference.

DISCUSSION

In this study, a similar reduction in HbA1c was observed after 26-month treatment of either exenatide or insulin glargine in patients with T2DM previously inadequately controlled with

Table 1. **Comparative baseline and 26-week data of study groups.**

	Group 1 (exenatide)		Group 2 (insulin glargine)	
	Baseline	Week 26	Baseline	Week 26
Patients (N)	18	18	29	29
Males/Females (N)	6/12	6/12	10/19	10/19
Age (years)	58.5 ± 8.0	–	64.1 ± 8.9	–
Duration of T2DM	10.4 ± 5.6	–	12.9 ± 8.0	–
BMI (kg/m^2)	39.9 ± 7.1	38.1 ± 6.6*	31.0 ± 4.7 ǂ	31.2 ± 4.4 ǂ
HbA1c (%)	8.6 ± 1.9	7.3 ± 1.1*	8.3 ± 1.4	7.8 ± 1.2*
Systolic blood pressure (mmHg)	150 ± 22	145 ± 21	141 ± 21	138 ± 17
Diastolic blood pressure (mmHg)	84 ± 8	86 ± 9	80 ± 11	79 ± 10
Total cholesterol (mg/dl)	205 ± 40	190 ± 40*	195 ± 58	178 ± 56*
LDL-cholesterol (mg/dl)	124 ± 35	113 ± 34*	113 ± 52	100 ± 46
HDL-cholesterol (mg/dl)	43 ± 6	46 ± 5*	53 ± 32	51 ± 18
Triglycerides (mg/dL)	230 ± 125	192 ± 110*	156 ± 78 ǂ	146 ± 64

Data are presented as mean ± standard deviation (SD) or as numbers and/or percentages
* p<0.05 compared to baseline (within groups comparison, paired-sample T-test or Wilcoxon signed ranks test)
ǂ p<0.05 compared to Group 1 (between groups comparison, independent samples T-test or Mann-Whitney test or Chi-square test)

metformin monotherapy. This reduction was independent of age and BMI at baseline. However, higher rate of patients achieved the glycemic goal of HbA1c < 7% in exenatide group. As expected, higher rate of hypoglycemia was observed in insulin glargine group. Gastrointestinal adverse events, mainly nausea, were transient and clinically non-significant. BMI reduction was observed in exenatide group, whereas BMI remained essentially unchanged in insulin glargine group. Comparable effects were observed in lipid profile in both groups, whereas neither agent had an effect on blood pressure.

Other head-to-head studies have provided similar results. In a 26-week, multicenter, open label, randomized trial, exenatide (10 μg twice daily) reduced HbA1c similarly to insulin glargine (once daily) [9]. Body weight decreased 2.3 kg with exenatide and increased 1.8 kg with insulin glargine. Nocturnal hypoglycemia occurred less frequently with exenatide, whereas gastrointestinal adverse events, including nausea, vomiting and diarrhea were more common in the exenatide group. In another 16-week multicenter, open-label, randomized, crossover study, treatment with either exenatide (10 μg twice daily) or insulin glargine (once daily) was associated with similar improvement in HbA1c, independent of treatment order [12], whereas only exenatide therapy was associated with significant reduction in body weight. In another 26-week multicenter, open-label, randomized trial, treatment, either exenatide (10 μg twice daily) or insulin glargine (once daily) failed to significantly decrease HbA1c. There were more treatment-related adverse events, but lower rate of nocturnal hypoglycaemia and greater efficacy in weight decrease with exenatide [11]. In a more recent 12-month, retrospective study based on a large electronic medical record database, greater reductions in HbA1c and BMI were observed in exenatide compared with insulin glargine-treated patients [10]. There is also a 84-week, multicenter, open label, randomized trial in which insulin glargine was compared to exenatide once weekly [13], which, however, is not currently widely available. Better glycemic control, sustained overall weight loss and a lower risk of hypoglycemia were reported in patients treated with exenatide weekly compared with insulin glargine [13].

Similar to our study, more patients in exenatide group achieved the goal set at three of the above mentioned studies: HbA1c < 7% [10]; HbA1c < 6.5% [13]; HbA1c ≤ 7.4% plus weight gain ≤ 1 kg [11]. On the other hand, equal proportion of patients in either group achieved HbA1c < 7% in the rest two studies [9, 12].

Similar to our findings, decrease in body weight after exenatide and increase after insulin glargine treatment are generally stable observations in the above mentioned head-to-head studies [9-13]. More episode of hypoglycemia in insulin glargine group, whereas more gastrointestinal adverse events in exenatide group are also stable observations, although not always statistically significant [9-13]. However, of the five head-to-head studies, only two assessed serum lipid profile [10, 11]. In one of them, there was similar non-significant decrease in triglycerides, total and LDL cholesterol in both groups, whereas HDL cholesterol remained essentially unchanged. In the other study, similar decrease in total cholesterol and triglycerides were reported in two groups, whereas LDL cholesterol was decreased only in exenatide group [11]. Contrary to our findings, three studies reported decrease in systolic blood pressure only in exenatide group [10, 11, 13]; however, none of them showed any effect of either agents on diastolic blood pressure. Differences in study populations and methodology may partly account for between studies differences. Therefore, more studies with the comparative effect on lipid profile or metabolic parameters as primary end-points are needed.

An important issue regarding either exenatide or insulin glargine is cost-effectiveness. Some authors reported that both are expensive to be second-line treatment for T2DM patients, but other authors suggest that early exenatide treatment may provide a potential for beta-cell proliferation, induction of islet neogenesis, and inhibition of beta-cell apoptosis, thus preserving and/or expanding β-cell mass and function [16]; early insulin treatment may also improve and preserve β-cell function and reduce diabetic complications [17]. Comparative studies regarding evaluation of cost effectiveness between exenatide and insulin glargine are conflicting. Some studies have reported that exenatide [18-20], whereas others insulin glargine [21, 22] is more cost-effective, when oral anti-diabetic drugs fail to achieve or sustain glycemic control in T2DM. Further studies are needed to elucidate whether exenatide or insulin glargine are cost-effective as second-line treatment for T2DM.

One advantage of our study was the fact that all patients had previously received only metformin. On the contrary, the patients of al the above head-to-head studies had been previously on combination with metformin and sulfonylurea therapy [9], or with any single [12] or combination oral anti-diabetic therapy [10, 11, 13]. The fact of its non-randomized and open label nature has probably resulted in selection and allocation biases; however, it simulates to real-world clinical practice, where exenatide is mainly proposed in obese diabetics, being in high hypoglycemic risk, before β-cell mass and function are eliminated [3-5]. Furthermore, we did not perform an a priori power analysis; however, a post-hoc power analysis for the between - within group interaction of the primary end-point (HbA1c), provided a post-hoc power of 84.1%, for type α error 0.05. Finally, by evaluating the comparative effect of either treatment on HbA1c, lipid profile, blood pressure and safety, we could not recommend either treatment as a second-line treatment after metformin in patients with T2DM. Further cost-effectiveness studies are required.

CONCLUSIONS

Exenatide provided similar reduction in HbA1c, but fewer episodes of hypoglycemia, compared with insulin glargine. Exenatide had also a favorable effect on weight loss, although more gastrointestinal adverse events. Exenatide may provide a justified alternative in second line treatment of T2DM, but more trials are required to elucidate its long-term safety and cost-effectiveness.

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