Exenatide's effect in reducing weight and glycosylated hemoglobin level in an Arab population with type 2 diabetes

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ABSTRACT

Objectives: To determine whether exenatide is effective in reducing weight and glycosylated hemoglobin level (HbA1c), and to investigate its efficacy in improving lipid profile, blood pressure, and creatinine levels in the Arab population.

Methods: This study was conducted at the Endocrine Unit, Dubai Hospital, Dubai, United Arab Emirates. We retrospectively collected data from patients with type 2 diabetes started on exenatide between November 2011 and February 2012. Data included demographics, clinical, laboratory results, and medications used. A general linear model adjusted by baseline characteristics (weight, HbA1C, age, use of statins, and duration of diabetes) was used to assess changes between baseline and end of trial in HbA1C, weight, low density lipoprotein cholesterol, total cholesterol, triglycerides, creatinine, and blood pressure.

Results: After 6 months of treatment with exenatide, the HbA1c decreased by 0.47% (95% confidence level [CI]: -0.01 - 0.95) (p=0.055). Weight reduction was highly significant; 5.6 kg (95% CI: 3.34 - 7.85) (p<0.001). Those reductions remained significant after adjustment for confounding factors.

Conclusion: This study showed that weight reduction was highly significant with exenatide. The borderline significance in HbA1c reduction can be attributed to the small sample size.

Historically all metabolic derangement recorded with diabetes was attributed to the absolute or relative deficiency of insulin, however in 1975 Unger's and Orci[1] suggested the so called "bi-hormonal theory," in which the relative or absolute deficiency of insulin, and relative or absolute excess of glucagon are both considered etiological factors. Insulin deficiency is responsible for the reduced utilization of glucose, while hyperglucagonemia is responsible for increased glucose production.[1] Incretin-based therapies represent a novel class of therapeutic agents for the treatment of type 2 diabetes that not only target deficits in insulin secretion, but also reduces postprandial glucose and glucagon levels. One of the major incretin hormones identified to date is the glucagon-like peptide-1 (GLP-1). The GLP-1 is secreted from the intestines in response to food ingestion. The effect of GLP-1 lasts for only a few minutes. They exert their effect through receptors that are located at different organs including the heart, the brain, pancreas, and kidneys.[2] It acts on pancreatic beta cells to stimulate insulin secretion in a glucose-dependent manner, and enhances insulin gene transcription and biosynthesis.[3] Moreover, preclinical studies have shown that GLP-1 can increase beta-cell mass via stimulation of beta-cell proliferation and neogenesis, and inhibition of beta-cell apoptosis.[4] The effect on alpha cells results in the inhibition of glucagon secretion, and hence reduces postprandial hyperglycemia. Extra pancreatic effects include delayed gastric emptying, and improvement of insulin sensitivity in patients with diabetes.[5] In addition, GLP-1 activates regions in the central nervous system that control satiety, and longer-term studies demonstrate that exogenous GLP-1 receptor agonist administration promotes satiety, and reduces body weight in diabetic patients.

Exenatide is the first discovered GLP-1 analogue. Several trials showed a dose dependent weight reduction of 1.6±0.5 kg in a 5 mcg dose, and 2.8±0.4 kg in a 10 mcg dose.[6] Better glycemic control was achieved when exenatide was combined with sulfonylurea or metformin, but the weight loss effect was not remarkably better than exenatide monotherapy.[7] When exenatide was combined with glargine and biphasic insulin therapies, the HbA1c was reduced by approximately 0.9%, and the weight was reduced by an average of 1.5 kg from baseline, moreover, the weight increment action of the insulins was abolished.[8,9] An extension of 172 weeks to this trial showed that the reduction in body weight with exenatide was 7.9 ± 1.8 kg (p<0.001).[10] On the other hand, another trial demonstrated that the longer the

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administration of exenatide, the greater the effect on HbA1c and weight, with a mean weight reduction of 4.4 kg after 3 years.[11] There is limited data to prove whether the effect of exenatide varies with race. The results of a post hoc analysis showed that the treatment of type 2 diabetes with exenatide for 24-30 weeks was associated with significant improvement in glycemic control and body weight, irrespective of race, however, the beneficial effect on systolic blood pressure (BP), and lipid profile was more important in white and Asian populations, while little benefit was observed in Hispanics, and no effect was noted in a black population.[12] Unfortunately, there are no studies directly addressing the efficacy GLP-1 analogues in an Arab population. In this study, we aim to retrospectively assess the efficacy of exenatide in reducing HbA1c and weight in an Arab population over 6-month period.

Methods. This retrospective study was conducted at the Endocrine Unit, Dubai Hospital Specialist Clinics, Dubai, United Arab Emirates. The study adhered to the tenets of the Declaration of Helsinki. The protocol was compliant with the Health Insurance Portability and Accountability Act, and approved by the institutional review board. As per local recommendations, no consent form was required for retrospective trials. The primary end point of the study was the mean change in HbA1c and in weight from baseline, and after 6 months of treatment. The changes in the lipid panel from baseline to the end of follow-up were analyzed as secondary end points, as were BP, and creatinine changes. All adult Arab patients (age between 18 and 70 years) with type 2 diabetes, who were started on exenatide (5 mcg twice per day subcutaneously for one month, followed by 10 mcg twice per day thereafter) in the period from November 2011 to February 2012 were recruited to the study. As the prescription of exenatide was compliant with the local recommendations; patients with type 1 diabetes, patients with severe renal impairment, or pregnant ladies were not prescribed exenatide. Furthermore, we excluded patients with incomplete files, and patients with contradicting data in files and electronic database. The data collection sheet included patients' demographics, co-morbidities, concurrent medications, weight, BP, a serum lipid profile (total cholesterol, low-density lipoprotein [LDL], triglycerides), and a serum chemistry test (fasting glucose, HbA1c, creatinine). These data were collected at baseline and at the end of the study (6 months). Data collected from files were crosschecked with the electronic data base (Software Management System [SAM System, Northland, Bay of Plenty, New Zealand]) to ensure accuracy.

Data analysis was performed using Statistical Package for Social Sciences for Windows version 17 (SPSS Inc. Chicago, IL, USA). In all analysis, $p<0.05$ was considered significant. A general linear model adjusted by baseline characteristics (weight, HbA1C, age, use of statins, and duration of diabetes) was used to assess changes between baseline and at 6 months in HbA1C, weight, LDL, total cholesterol, triglycerides, creatinine, and BP.

Results. *Patients.* A total of 62 patients were recruited. Eight have been excluded as 2 patients had contradicting data in their files compared to the electronic SAM system; another 3 had incomplete files, and the remaining 3 did not complete the treatment for 6 months because of the side effects (nausea and vomiting). The baseline characteristics of all 54 patients who were included in the final analysis are shown in **Table 1**. The mean age was 50.59 (±11.1) years, and the mean duration of diabetes was 11.81 (±7.1) years. They were obese patients (103.2 kg mean weight) with a mean HbA1c of 9.234%. Most patients had their BP controlled (mean SBP was 136 mm Hg and mean DBP was 76.7 mm Hg) in addition to their lipid profile with a mean LDL of 89.39 mg/dL.

Efficacy. **Table 2** shows the comparison of baseline and end of trial characteristics of the participants.

Table 1 - Baseline characteristics of the study participants in a study on an Arab population.

Variables	Results
Total number of patients	54
Age, years	
<40	9
40-59	36
≥60	9
Gender, n (%)	
Male	14 (26.0)
Female	40 (74.0)
Mean weight, kg	103.2
Mean glycosylated hemoglobin level (%)	(9.234)
Mean lipid profile (mg/dl)	
Total cholesterol	168.4
Low-density lipoprotein	89.38
Triglycerides	163.5
Mean blood pressure (mm Hg)	
Systolic	136
Diastolic	76.7
Mean creatinine (mg/dl)	0.8736

Table 2 - Comparison of baseline and end of trial characteristics of participants in a study on an Arab population.

Variables	Baseline characteristics n=54 (%)	At 6 months	*P*-value
Age, years	50.59 (11.1)		
Glycosylated hemoglobin level (%)	9.23 (2.1)	8.75 (2.1)	0.055
Weight, kg	103.16 (2.1)	97.57 (18.3)	<0.001
Total cholesterol	170.80 (41.3)	169.80 (46.7)	0.86
Low-density lipoprotein	90.69 (33.7)	86.67 (41.0)	0.42
Triglycerides	163.29 (66.6)	163.76 (72.8)	0.95
Creatinine (mg/dl)	0.87 (0.2)	0.84 (24.0)	0.16
Systolic blood pressure (mm Hg)	136.04 (18.0)	133.51 (17.6)	0.32
Diastolic blood pressure (mm Hg)	76.68 (12.6)	75.59 (12.1)	0.55
Duration of diabetes, years	11.81 (7.1)		

After 6 months of treatment with exenatide, HbA1c decreased by 0.47% (95% CI: -0.01 - 0.95), (p=0.055). After correction for possible confounding factors that include age, weight, and HbA1c at baseline, as well as, the duration of diabetes on the change in HbA1c, the reduction in HbA1c remained non-significant. Mean weight reduction at the end of the trial was highly significant; 5.60 kg (95% CI: 3.34 - 7.85) (p< 0.001). This remained significant even after correction for confounding factors. We tested the effect of age, HbA1c, and weight at baseline, and the duration of diabetes on the change in weight, the weight reduction remained significant. The concomitant use of medications was also assessed; 83.3% (n=45) were concomitantly using metformin, 64% (n=35) were on insulin, 40.7% (n=22) were on sulphonylureas, 29.6% (n=16) were on DPPI, 9.2% (n=5) were on Acarbose, and only 2 patients were on thiazolidinediones (TZDs). There was no significant change in total cholesterol, LDL, and triglycerides observed between the baseline and the end of trial even after correction for the confounding factors. We also did not observe changes in the creatinine level and blood pressure (systolic and diastolic) between the start and the end of the trial.

Discussion. Exenatide is a GLP-1 mimetic that was proven to be effective in reducing HbA1c, fasting, and to more extent post prandial blood glucose. Moreover, exenatide's effect in reducing weight was an added value to the management of type 2 diabetes patients who are mostly overweight, or obese. This group of patients represented the first encounter for our physicians with the prescription of a GLP1 analogue that explains the small number of patients, and the late introduction of exenatide into the therapeutic regimen. These beneficial effects were demonstrated in many large studies.

In the AMIGO trial[6,7,11] performed on 1440 type 2 diabetes patients, 450 of them received a 10 mcg dose, and the average HbA1c reduction was 0.78-0.86%. The HbA1c reduction in our study was 0.47%. However, weight loss is more significant in our cohort, the mean weight loss was 5.6 kg compared with 1.6-2.8 kg in the registration trials. This difference in weight loss might be explained by the elevated baseline weight (103.2 kg) in our population. Many studies have shown that exenatide is effective in reducing HbA1c. However, exenatide effect in reducing HbA1c in our cohort was not significant, an explanation could be the small sample size that makes our study underpowered to assess the change in HbA1c over this short period of time. Another reason is the duration of diabetes; some data have shown that the shorter the duration of diabetes, the better the response.[13] The mean duration of diabetes in our study was 11.81 years. By this time, patients would have lost almost all beta cell functions, and hence, much of the benefits related to GLP1 analogues that acts partly by stimulating beta cell release of insulin. This fact was clearly demonstrated in our cohort as 64.8% of patients were already on insulin, which is generally started late in the course of the disease. The final factor that was found to influence response to exenatide is the baseline HbA1c level, the lower the HbA1c, the better the response. In our study, the baseline HbA1c was high 9.2%.

Limitations of the study. The retrospective design of the study and small sample size were the major limitation. The sample size may have had an influence on the HbA1c results, but other factors like disease duration use of insulin and high baseline HbA1c might have affected the results.

In conclusion, the months treatment with exenatide resulted in significant weight reduction, but the effect on HbA1c, lipid profile, BP, and creatinine were not significant. The effect on HbA1c could be explained by the small sample size and the long duration of diabetes at baseline. We recommend a larger randomized controlled trial to assess the effect of exenatide in an Arab population, as well as the pattern of prescription of the GLP1 analogues in the Gulf region.

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