

CLINICAL USE OF LIRAGLUTIDE IN TYPE 2 DIABETES AND ITS EFFECTS ON CARDIOVASCULAR RISK FACTORS

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ABSTRACT

Objective: To assess whether liraglutide, a glucagon-like peptide-1 receptor agonist, has cardioprotective properties in addition to its glycemic effects.

Methods: We performed a retrospective analysis of medical records of 110 obese patients with type 2 diabetes mellitus treated with liraglutide for at least 6 months between March 2010 and April 2011 at our tertiary care referral center. The variables analyzed were body mass index, hemoglobin A_{1c} (A1C), systolic blood pressure (SBP), plasma C-reactive protein (CRP) concentrations, and serum lipids.

Results: In our overall study cohort, we noted a reduction in mean weight from 120 ± 5 kg to 115 ± 3 kg and a decrease in mean A1C from $7.8\% \pm 0.6\%$ to $7.2\% \pm 0.2\%$. The mean triglyceride concentration decreased from 173 ± 19 mg/dL to 151 ± 15 mg/dL, the mean SBP was reduced from 132 ± 6 mm Hg to 125 ± 4 mm Hg, and the mean CRP concentration declined from 4.7 ± 0.8 mg/L to 3.2 ± 0.4 mg/L after treatment with liraglutide for a minimal duration of 6 months and a mean duration of 7.5 months (for all the foregoing changes, $P < .05$). These variables decreased

whether these patients were previously treated with orally administered hypoglycemic agents alone or in combination with insulin or exenatide.

Conclusion: Our findings in a clinical practice show that liraglutide is a potent antidiabetes drug, whether given in combination with orally administered agents or insulin or as a substitution for exenatide. It lowers body weight, A1C levels, SBP, and CRP and triglyceride concentrations. (Endocr Pract. 2012;18:140-145)

Abbreviations:

A1C = hemoglobin A_{1c}; **BMI** = body mass index; **CRP** = C-reactive protein; **GLP-1** = glucagonlike peptide-1; **SBP** = systolic blood pressure

INTRODUCTION

Liraglutide is a glucagonlike peptide-1 (GLP-1) receptor agonist, which has been in use in patients with type 2 diabetes for approximately 1 year. It exerts its action through (1) stimulation of insulin secretion in a glucose-dependent manner, (2) suppression of glucagon, (3) reduction of appetite and food intake, and (4) deceleration of gastric emptying. In addition, it leads to weight loss (1-6).

We described 2 novel effects of exenatide, the first GLP-1 agonist in clinical use, in 2007: a significant reduction in plasma C-reactive protein (CRP) concentrations and a reduction in systolic blood pressure (SBP). In addition, it lowered plasma triglyceride concentrations (7). These data were obtained from patients being treated with a combination of insulin and exenatide, a combination not hitherto approved by the US Food and Drug Administration. During a long-term follow-up study, we confirmed the continuation of these effects of exenatide (8).

In view of the fact that liraglutide is also a stimulator of GLP-1 receptor, it is possible that this drug has SBP-lowering properties (9). Indeed, these effects have been confirmed for liraglutide in randomized controlled studies in patients with type 2 diabetes (2,10).

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This retrospective study describes the glycemic effects of liraglutide along with its SBP-, CRP-, and triglyceride-lowering properties in patients with type 2 diabetes treated in a tertiary referral center because there are no available data from such patients outside the setting of randomized clinical trials. In addition, this report presents data related to the use of liraglutide in conjunction with insulin for the first time.

PATIENTS AND METHODS

This is a retrospective review of medical records of 110 patients with type 2 diabetes mellitus who are being treated with liraglutide at the Diabetes Center of Western New York, a tertiary care referral center. Institutional review board approval was obtained for the retrospective analysis and the study to be performed. These patients were prescribed liraglutide because they were obese, had uncontrolled hyperglycemia, and continued to gain weight despite being treated with orally administered agents either alone or in combination with insulin. We screened the medical records of patients who were treated with liraglutide between March 2010 and April 2011. To be included in the study, patients must have taken liraglutide for at least 6 months. All patients met with our diabetes educators when liraglutide therapy was initiated. Patients were also given the opportunity to meet with a dietitian as part of their routine management of diabetes. Lifestyle changes that moderately decrease the intake of calories (250 to 500 kcal daily) and increase energy expenditure were strongly encouraged. Patients were advised to begin and continue a program of weight control, including at least 150 minutes per week of moderate to vigorous physical activity.

Patients were initially given liraglutide, 0.6 mg a day. The dosage was increased to 1.2 mg daily after 2 weeks, if patients tolerated the initial dose and if the response to the initial dose was inadequate. The dosage of liraglutide was further increased to 1.8 mg/d after 2 more weeks in patients who tolerated the 1.2-mg daily dose. Patients were examined every 2 to 12 weeks, with the interval based on clinical evaluation at each visit. Hemoglobin A_{1c} (A1C) levels were measured at baseline (before starting liraglutide therapy) and during the clinic visit every 3 months. Weight and blood pressure were measured at baseline and at every clinic visit. Fasting lipid and CRP concentrations were measured at baseline and subsequently at the discretion of the treating physician. For measurement of CRP, a nephelometric method utilizing latex particles coated with CRP monoclonal antibodies was used (Quest Diagnostics). This assay has a sensitivity of 0.2 mg/dL, an intra-assay coefficient of variation of 4.4%, and an interassay coefficient of variation of 5.7%.

At the time of initiation of liraglutide therapy, study patients were receiving the following other diabetes treatments: insulin in 65, metformin in 102, sulfonylureas in

54, thiazolidinediones in 38, and sitagliptin in 18. Other therapies at baseline were antihypertensive medications in 104 patients, statins in 92, fibrates in 34, and niacin in 22. Angiotensin-converting enzyme inhibitors were taken by 76 patients, hydrochlorothiazide by 56, β -adrenergic blocking agents by 47, and calcium channel blockers by 28. Changes in blood pressure and lipid levels after initiation of liraglutide therapy are reported only in patients whose medications were not changed.

We also analyzed data on 22 of the 110 patients whose treatment was switched from exenatide to liraglutide at the discretion of the treating physician. The reasons for this change were the absence of further weight loss, no further decrease in A1C, or further weight gain while receiving a maximal dose of exenatide. These patients had taken exenatide for a mean duration of 14 ± 2 months.

Statistical comparison for various indices was performed with use of paired *t* tests for parametric data and the Wilcoxon signed rank test for nonparametrically distributed paired data. Spearman correlation (for data not normally distributed) and Pearson correlation (for normal data) tests were used, as appropriate, to establish correlations. Multiple regression analyses with use of a backward stepwise regression model between variables were performed if there were 2 or more independent variables. *P* values $<.05$ were considered significant. SPSS software (SPSS Inc., Chicago, Illinois) was used to perform the analysis. All data are reported as mean values $\pm$ standard error of the mean.

RESULTS

The mean duration of liraglutide use was 7.5 months (range, 6 months to 1.1 years). Eight patients discontinued liraglutide treatment; contributing factors were side effects, including incessant mild nausea in 5 patients, and lack of insurance coverage or financial reasons in 3 patients. None of the patients treated with liraglutide had pancreatitis or severe hypoglycemic episodes that necessitated assistance during the study duration.

Results for the Entire Group

In the overall study group of 110 patients, there was a reduction in mean weight from 120 ± 5 kg to 118 ± 3 kg after 3 months of liraglutide therapy ($P = .04$) and a further reduction of 3 kg during the next 3 months ($P < .001$). In addition, mean A1C was reduced by 0.25% from $7.8\% \pm 0.6\%$ to $7.55\% \pm 0.3\%$ ($P = .03$) after the first 3 months of treatment with liraglutide and showed a further reduction by 0.35% to 7.2% during the next 3 months ($P < .001$). The mean triglyceride concentration decreased from 173 ± 19 mg/dL to 151 ± 15 mg/dL in 6 months ($P = .02$). The mean SBP decreased from 132 ± 6 mm Hg to 127 ± 4 mm Hg after the first 3 months of liraglutide treatment ($P = .03$), and there was a further decline by 2 mm Hg at 6 months

($P < .001$). A significant reduction in mean CRP concentration was noted from 4.7 ± 0.8 mg/L to 4.0 ± 0.6 mg/L ($P = .03$) at 3 months, and there was a further reduction to 3.2 ± 0.4 mg/L at 6 months ($P = .02$). No significant change occurred in diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and urine microalbumin/creatinine ratio (Table 1).

The decline in mean SBP was maximal during the first 3 months after initiation of liraglutide treatment— 5 ± 2 mm Hg; the decrease was 2 ± 0.5 mm Hg during the next 3 months. In contrast, the mean weight loss was greater during the second 3 months of liraglutide therapy. The decline in SBP was not related to the decrease in weight ($r = 0.22$; $P = .24$), triglycerides ($r = 0.19$; $P = .28$), A1C ($r = 0.15$; $P = .33$), or CRP ($r = 0.18$; $P = .30$). The decrease in mean CRP concentration was unrelated to the change in weight ($r = 0.28$; $P = .12$). On multiple regression analysis, the change in CRP value was independently related to the change in A1C ($\beta = 0.36$; $P < .001$) and the change in triglyceride concentration ($\beta = 0.26$; $P = .03$). There was a significant relationship between the reduction in CRP concentration and baseline CRP ($r = 0.67$; $P < .001$), reduction in A1C ($r = 0.68$; $P < .001$), and decrease in triglyceride level ($r = 0.48$; $P = .03$). Change in CRP was not related to change in weight ($\beta = 0.08$; $P = .26$) or SBP ($\beta = 0.06$; $P = .34$; R^2 of the model 0.19). The relationship between triglyceride reduction and A1C reduction was significant ($r = 0.42$; $P = .03$). The reduction in triglyceride concentrations was not related to the change in weight ($r = 0.24$; $P = .26$).

Subgroup Analysis of Patients Receiving Insulin

In our overall series of 110 patients who were treated with liraglutide, 65 patients were already receiving insulin. In this subgroup, there was a reduction in mean weight from 122 ± 4 kg to 120.5 ± 3 kg after 3 months of liraglutide therapy ($P = .06$), and a further reduction of 2.5 kg occurred during the next 3 months ($P = .04$). The mean A1C decreased by 0.3% from $7.5\% \pm 0.4\%$ to $7.2\% \pm 0.3\%$ ($P = .02$) after the first 3 months, and there was a further reduction of 0.1% during the next 3 months (not significant). The mean plasma triglyceride concentration declined from 163 ± 11 mg/dL to 146 ± 9 mg/dL after 6 months of liraglutide treatment ($P = .04$). The mean SBP decreased from 129 ± 5 mm Hg to 125 ± 4 mm Hg after the first 3 months ($P = .03$), and there was an overall reduction of 5 mm Hg by 6 months after onset of liraglutide therapy ($P = .03$). There was a significant reduction in mean CRP concentration from 4.3 ± 0.5 mg/L to 3.3 ± 0.3 mg/L ($P < .001$) after 3 months; a further reduction to 3.0 ± 0.2 mg/L was noted at 6 months. These improvements were associated with a reduction in the total dose of insulin by

Table 1
Results in 110 Patients Who Received Liraglutide for a Mean Duration of 7.5 Months^a

Factor	At onset of liraglutide	At 3 mo	P value	At 6 mo	P value compared with	
					3 Mo	Baseline
Weight (kg)	120 ± 5	118 ± 3	.04	115 ± 3	<.001	<.001
Body mass index (kg/m ²)	38.2 ± 4	37.5 ± 3	.04	36.5 ± 3	<.001	<.001
Hemoglobin A _{1c} (%)	7.8 ± 0.6	7.55 ± 0.3	.03	7.2 ± 0.2	<.001	<.001
Triglycerides (mg/dL)	173 ± 19	159 ± 16	.11	151 ± 15	.16	.02
Cholesterol (mg/dL)						
Total	198 ± 20	193 ± 20	.21	191 ± 18	.34	.18
High-density lipoprotein	38 ± 2	39 ± 2	.32	39.5 ± 2	.38	.34
Low-density lipoprotein	95 ± 4	92 ± 3	.22	93 ± 3	.31	.27
Blood pressure (mm Hg)						
Systolic	132 ± 6	127 ± 4	.03	125 ± 4	.11	<.001
Diastolic	79 ± 2	77 ± 2	.21	76.8 ± 1	.32	.20
C-reactive protein (mg/L)	4.7 ± 0.8	4.0 ± 0.6	.03	3.2 ± 0.4	.02	<.001
Urine microalbumin/creatinine ratio (μg/mg)	18 ± 3	17 ± 2	.28	16.5 ± 2	.49	.26

^a Twenty-two patients who had a change in lipid-lowering drugs and 24 patients who had a change in antihypertensive drugs were excluded from total, high-density lipoprotein, and low-density lipoprotein cholesterol, triglyceride, and blood pressure analyses mentioned in this table.

18.6% during liraglutide treatment (Table 2). The premeal insulin dose decreased from 40 ± 4 U to 31 ± 3 U ($P < .001$), whereas the basal insulin dose decreased from 46 ± 4 U to 39 ± 3 U ($P = .03$). No significant change occurred in diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and urinary microalbumin/creatinine ratio (Table 2).

Subgroup Analysis of Patients Who Were Switched From Exenatide to Liraglutide Treatment

In our study cohort, 22 patients were switched from exenatide to liraglutide therapy. These patients had gained a mean of 1 ± 0.5 kg in body weight during the 3 months before this change to liraglutide treatment. After the onset of liraglutide therapy, these patients lost a mean of 3 ± 1 kg in 6 months ($P < .001$). The mean A1C value was reduced 0.3% after 6 months of treatment with liraglutide ($P = .022$). Moreover, there was a significant decrease in SBP of 4 mm Hg ($P = .04$). There was no further significant reduction in CRP and triglyceride concentrations (Table 3).

DISCUSSION

Our data clearly show that liraglutide significantly reduced the A1C levels, body weight, CRP and triglyceride concentrations, and SBP in the entire population of patients with type 2 diabetes studied. In assessment of patients with type 2 diabetes already receiving treatment with insulin, the initiation of liraglutide therapy led to a significant decrease in body weight, A1C, SBP, and triglyceride and CRP concentrations, as observed previously with exenatide. Thus, the changes in this group also demonstrated a reversal of features of the metabolic syndrome. Switching from exenatide to liraglutide treatment is well tolerated and provides additional glycemic control and cardiometabolic benefits (11). Those patients in our study who were converted to liraglutide from exenatide therapy also experienced a significant reduction in body weight, A1C, and SBP but did not have a significant further reduction in CRP concentration. There was a trend toward a decline in triglyceride concentrations, but this change was short of

Table 2
Results in 65 Patients Who Were Treated With Liraglutide and Were Already Receiving Insulin^a

Factor	At onset of liraglutide	At 3 mo	P value	At 6 mo	P value compared with	
					3 Mo	Baseline
Weight (kg)	122 ± 4	120.5 ± 3	.06	118	.04	<.001
Body mass index (kg/m ²)	38.7 ± 4	38.1 ± 3	.06	37.2 ± 3	.04	<.001
Hemoglobin A _{1c} (%)	7.5 ± 0.4	7.2 ± 0.3	.02	7.1 ± 0.2	.12	.02
Triglycerides (mg/dL)	163 ± 11	152 ± 9	.09	146 ± 9	.14	.04
Cholesterol (mg/dL)						
Total	199 ± 18	196 ± 16	.38	192 ± 12	.32	.22
High-density lipoprotein	40 ± 2	41 ± 2	.31	41.4 ± 3	.52	.29
Low-density lipoprotein	82 ± 4	76 ± 3	.31	74 ± 5	.43	.18
Blood pressure (mm Hg)						
Systolic	129 ± 5	125 ± 4	.03	124 ± 4	.11	.03
Diastolic	81 ± 2	80 ± 2	.24	80 ± 3	.38	.27
Insulin dose (U)	86 ± 8	72 ± 6	<.001	70 ± 5.2	.42	<.001
Basal	46 ± 4	40 ± 3	.04	39 ± 3	.66	.03
Bolus	40 ± 4	32 ± 2	<.001	31 ± 3	.49	<.001
C-reactive protein (mg/L)	4.3 ± 0.5	3.3 ± 0.3	<.001	3.0 ± 0.2	.22	<.001
Urine microalbumin/creatinine ratio (μg/mg)	18 ± 3	16 ± 2	.29	15.5 ± 2	.44	.26

^a Fourteen patients who had a change in lipid-lowering drugs and 10 patients who had a change in antihypertensive drugs were excluded from total, high-density lipoprotein, and low-density lipoprotein cholesterol, triglyceride, and blood pressure analyses mentioned in this table.

Table 3
Results in 22 Patients Who Were Switched From Exenatide to Liraglutide Therapy

Factor	Receiving exenatide	At onset of liraglutide	P value	At 6 mo	P value
Weight (kg)	117 ± 4	118 ± 4	.15	115 ± 3	<.001
Body mass index (kg/m ²)	38.0 ± 3	38.3 ± 4	.15	36.2 ± 3	<.001
Hemoglobin A _{1c} (%)	7.65 ± 0.5	7.6 ± 0.5	.31	7.3 ± 0.4	.022
Triglycerides (mg/dL)	158 ± 14	154 ± 14	.26	144 ± 13	.08
Cholesterol (mg/dL)					
Total	202 ± 18	197 ± 17	.28	191 ± 26	.13
High-density lipoprotein	41 ± 1	41.4 ± 1	.34	41 ± 1	.38
Low-density lipoprotein	92 ± 6	91 ± 5	.44	85 ± 4	.26
Blood pressure (mm Hg)					
Systolic	127 ± 4	128 ± 4	.42	124 ± 3	.04
Diastolic	84 ± 3	83 ± 3	.36	81 ± 2	.34
C-reactive protein (mg/L)	2.8 ± 0.6	2.9 ± 0.5	.46	2.5 ± 0.4	.12

statistical significance. These observations are important because they confirm the presence of the beneficial effects of this drug not only from the glycemic point of view but also from the standpoint of potential prevention of cardiovascular disease. Although most of these effects have previously been described in randomized control trials, this study is the first one from an actual clinic setting that confirms the presence of these effects. These data, however, are the first to reveal the effects of adding liraglutide to insulin treatment in patients with type 2 diabetes.

Although the mechanisms underlying the decrease in glucose concentrations include the increase in postprandial insulinogenesis and glucagon suppression, the suppression of appetite, and the slowing of gastric emptying (12), those related to the reduction of SBP, triglycerides, and CRP are not clear. Weight loss is clearly related to the suppression of appetite induced by liraglutide, consistent with the action of GLP-1 (13). The decline in CRP is consistent with our original observation in 2007, when we reported on a similar effect of exenatide (7). This decrease is independent of weight loss and is probably the consequence of a comprehensive antiinflammatory action, as observed with exenatide (14-16). This area needs further investigation. The decrease in triglyceride concentration may be mediated by increased insulinogenesis, inasmuch as insulin suppresses triglyceride synthesis in the liver. In addition, it is possible that GLP-1 agonists may exert a similar independent effect of their own (17).

The isolated decrease in SBP in the absence of a change in diastolic blood pressure may be attributable to an increase in arterial compliance and a decrease in arterial stiffness (18). The fact that there was a decrease in body mass index (BMI), A1C, SBP, triglycerides, and CRP in

patients taking insulin reflects an improvement in glycemic and appetite control and a potential antiinflammatory effect of liraglutide. Because the decrease in CRP was related to the reductions in A1C and triglycerides, and the reduction of triglyceride concentration was related to A1C on multivariate analysis, it seems that the improved glycemic control was the key to these effects. Of interest, neither the decrease in the CRP concentration nor the reduction of the SBP was related to the change in BMI. Of note, the change of treatment from exenatide to liraglutide resulted in further significant reductions in BMI, A1C, and SBP. This difference may be due to the fact that the 2 daily injections of exenatide do not provide therapeutic concentrations of this drug around the clock, whereas a single injection of liraglutide per day does (10). Compliance with a 2-injection daily regimen is also more difficult. In addition, patients who switched from exenatide to liraglutide had a further effect on weight loss, possibly because these GLP-1 receptor agonists work on different parts of the hindbrain.

Reductions in risk factors or markers for cardiovascular disease, such as plasminogen activator inhibitor-1 and brain natriuretic peptide, have also been observed after treatment with liraglutide (17). This study showed a non-significant, but dose-dependent, reduction in high-sensitivity CRP levels. Decreases in triglyceride concentrations of 20% or more have been reported with liraglutide treatment (17).

CONCLUSION

Liraglutide exerts several beneficial effects including an improvement in glycemic control and a reduction in body weight, SBP, and the plasma concentrations of CRP

and triglycerides. These actions indicate the ability of liraglutide to reverse the features of the metabolic syndrome and several cardiovascular risk factors. Liraglutide and other GLP-1 agonists offer a series of novel factors in the treatment of type 2 diabetes which not only yield glycemic control but also potentially reduce cardiovascular risk.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

REFERENCES

1. **Bode B.** Liraglutide: a review of the first once-daily GLP-1 receptor agonist. *Am J Manag Care.* 2011;17(2 suppl):S59-S70.
2. **Astrup A, Rössner S, Van Gaal L, et al (NN8022-1807 Study Group).** Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study [published correction appears in *Lancet.* 2010;375:984]. *Lancet.* 2009;374:1606-1616.
3. **Nauck M, Frid A, Hermansen K, et al (LEAD-2 Study Group).** Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (Liraglutide Effect and Action in Diabetes)-2 study. *Diabetes Care.* 2009;32:84-90.
4. **Zinman B, Gerich J, Buse JB, et al (LEAD-4 Study Investigators).** Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD) [published correction appears in *Diabetes Care.* 2010;33:692]. *Diabetes Care.* 2009;32:1224-1230.
5. **Gallwitz B, Vaag A, Falahati A, Madsbad S.** Adding liraglutide to oral antidiabetic drug therapy: onset of treatment effects over time. *Int J Clin Pract.* 2010;64:267-276.
6. **Jendle J, Nauck MA, Matthews DR, et al (LEAD-2 and LEAD-3 Study Groups).** Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue. *Diabetes Obes Metab.* 2009;11:1163-1172.
7. **Viswanathan P, Chaudhuri A, Bhatia R, Al-Atrash F, Mohanty P, Dandona P.** Exenatide therapy in obese patients with type 2 diabetes mellitus treated with insulin. *Endocr Pract.* 2007;13:444-450.
8. **Varanasi A, Chaudhuri A, Dhindsa S, et al.** Durability of effects of exenatide treatment on glycemic control, body weight, systolic blood pressure, C-reactive protein, and triglyceride concentrations. *Endocr Pract.* 2011;17:192-200.
9. **Okerson T, Chilton RJ.** The cardiovascular effects of GLP-1 receptor agonists [published online ahead of print December 19, 2010]. *Cardiovasc Ther.* doi:10.1111/j.1755-5922.2010.00256.x.
10. **Buse JB, Rosenstock J, Sesti G, et al (LEAD-6 Study Group).** Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet.* 2009;374:39-47.
11. **Buse JB, Sesti G, Schmidt WE, et al (Liraglutide Effect and Action in Diabetes-6 Study Group).** Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. *Diabetes Care.* 2010;33:1300-1303.
12. **Jellinger PS.** Focus on incretin-based therapies: targeting the core defects of type 2 diabetes. *Postgrad Med.* 2011;123:53-65.
13. **Hallberg P, Schwan S, Melhus H.** Liraglutide for weight loss in obese people [with author reply]. *Lancet.* 2010;375:551-553.
14. **Wu JD, Xu XH, Zhu J, et al.** Effect of exenatide on inflammatory and oxidative stress markers in patients with type 2 diabetes mellitus. *Diabetes Technol Ther.* 2011;13:143-148.
15. **Derosa G, Maffioli P, Salvadeo SA, et al.** Exenatide versus glibenclamide in patients with diabetes. *Diabetes Technol Ther.* 2010;12:233-240.
16. **Chaudhuri A, Ghanim H, Vora M, et al.** Exenatide exerts a potent anti-inflammatory action. Presented at: American Diabetes Association 71st Annual Meeting and Scientific Sessions; June 24-28, 2011; San Diego, CA. Abstract 970-P.01-D.
17. **Courrèges JP, Vilsbøll T, Zdravkovic M, et al.** Beneficial effects of once-daily liraglutide, a human glucagon-like peptide-1 analogue, on cardiovascular risk biomarkers in patients with type 2 diabetes. *Diabet Med.* 2008;25:1129-1131.
18. **Dandona P, Chaudhuri A, Dhindsa S.** A novel anti-hypertensive effect of exenatide, a GLP-1 agonist. *Am J Hypertens.* 2010;23:228.