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Beginning with very low dose (0.2mg) liraglutide in Indian type 2 diabetic patients appears better tolerated: experience from real life practice

Abstract

Background: The gastrointestinal (GI) intolerance is important deterrents to adherence and long-term compliance of liraglutide, a human glucagon-like peptide-1 (GLP-1) receptor agonist. To overcome this troublesome adverse effect, liraglutide in 0.2mg per day was used as starting dose and weekly up-titrated to 0.6mg per day.

Aim: To assess the efficacy and tolerability of very low dose (0.2mg) liraglutide versus usual dose (0.6mg) liraglutide as a starting dose in obese uncontrolled longstanding Indian type 2 diabetes patients (T2D).

Settings and design: A single centered, retrospective observational study conducted for 24weeks in a real-world setting.

Methods and material: Cohort A (n=32) comprised of the patients who received liraglutide in 0.6mg per day as starting dose and were treated during 2010-2012. Cohort B (n=31) comprises the patients who received liraglutide 0.2mg per day as starting dose and weekly up-titrated to 0.6mg per day and were treated during 2013-2015. Both cohorts were continued with liraglutide depending on clinical response, tolerability and affordability. All patients were evaluated at baseline and after 12 and 24weeks of therapy. Physical examination (height, body weight and body mass index [BMI]) and glycemic parameters (fasting plasma glucose [FPG], postprandial plasma glucose [PPG] and glycosylated hemoglobin [HbA1C]), were repeated and evaluated. Hypoglycemic events were recorded. Tolerability of liraglutide and the dropouts in every schedule visit was assessed.

Statistical analysis used: Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD and results on categorical measurements are presented in Number (%). Significance is assessed at a level of 5%. Unpaired t-test has been used to find the significance of study parameters between the two cohorts on continuous scale. Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two cohorts. Paired t-test was used to find any significant within group changes between baseline and at 24weeks.

Results: There was no statistical difference in baseline age, duration of diabetes, height, weight, BMI, diastolic blood pressure (DBP), systolic blood pressure (SBP), FPG, PPG and HbA1c between Cohort A and Cohort B. After 24weeks, there was no statistically significant reduction of HbA1c, FPG and PPG in either cohort but a significant reduction was observed in body weight and BMI in both cohorts. The absolute and relative body weight reduction was higher in the cohort A than cohort B, but the corresponding reduction in BMI was numerically higher in cohort B. Number of patients continuing liraglutide beyond 24weeks was much higher with cohort B (15 subjects, 48.39%) than cohort A (8 subjects, 25%) and the difference was very close to statistical significance (p value 0.069).

Conclusion: Starting with a very low dose (0.2mg) liraglutide with weekly up-titration appears better tolerated compared to optimal dose (0.6mg). An adequately powered prospective study is required to establish this benefit.

Keywords:very low dose liraglutide, tolerability, low dose liraglutide, India, type 2 diabetes

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Keymessages: Clinicians may start with very low dose (0.2mg per day) liraglutide with subsequent weekly up-titration to minimize the gastrointestinal intolerance of liraglutide therapy, in obese and/or overweight Indian type 2 diabetes patients.

Abbreviations: ADA, american diabetes association; BMI, body mass index; DBP, diastolic blood pressure; EASD, european association for the study of diabetes; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; GI, gastrointestinal; HbA1C, glycosylated hemoglobin; LEAD, liraglutide effect and action in diabetes; LEADER, liraglutide effect and action in diabetes: Evaluation of Cardiovascular outcome results; PPG, postprandial plasma glucose

Introduction

Liraglutide is a human GLP-1 analog and acts as a GLP-1 receptor agonist. GLP-1 receptor agonist based therapy stimulates insulin secretion, reduces glucagon secretion, slows gastric emptying and

reduces appetite.[1] Liraglutide is a once-daily human GLP-1 analogue with 97% linear amino-acid sequence homology to human GLP-1[2] and half-life of 13hours after subcutaneous administration that produces 24hour blood glucose control.[3] In our experience, 0.6mg once a day liraglutide therapy improved glycemic control and reduced weight, in obese uncontrolled long standing T2D. However, a significant proportion of patients dropped out because of GI intolerance.[4] The GI intolerance in our real world observational study was higher than LEAD (Liraglutide Effect and Action in Diabetes) study.[5] T2D is growing fast in India with more than 70million individuals currently diagnosed with the disease. A positive association between gain in weight and the risk of developing T2D has been established repeatedly in many studies.[6] It is also established, that for a given BMI, Asian Indians have higher fat percentage compared with Caucasian subjects.[7] Since T2D is obesity dependent, and obesity is the main etiogical cause of T2D, we should focus on managing the twin issues together. Liraglutide was launched in India barely months after its launch in the USA in 2010. During the initial years (2010-2012), we have used liraglutide in 0.6mg per day as starting dose and continued the therapy depending on clinical response, tolerance and affordability. Obese and overweight patients with T2D are good candidates for liraglutide therapy. However, GI intolerance remained the limiting factor associated with this therapy, but appears transient and can be minimized with gradual dose titration.[8] To overcome this troublesome adverse effect, during the last few years (2013-2015), Liraglutide in 0.2mg per day was used as starting dose and weekly up-titrated to 0.6mg per day. In the present study, we compared the tolerability and effectiveness of these two cohorts of liraglutide therapy in overweight or obese Indian T2DM patients.

Materials and methods

A single centered, retrospective observational, real world study conducted for 24weeks in the Endocrine out-patient department (OPD) of KPC Medical College. KPC Medical College is a 650 bedded, multispecialty hospital in Eastern part of India, having a dedicated Endocrine Clinic. Cohort A comprises the patients who received liraglutide in 0.6mg per day as starting dose and were treated during 2010-2012. Cohort B comprises the patients who received liraglutide 0.2mg per day as starting dose and weekly up-titrated to 0.6mg per day and were treated during 2013-2015. Both cohorts were continued on liraglutide depending on clinical response, tolerability and affordability. All patients received liraglutide in addition to existing anti-diabetic therapy except dipeptidyl peptidase-4 inhibitors and insulin. All were evaluated at baseline and after 12 and 24weeks of therapy. Physical examination (height, body weight & BMI) and glycemic parameters (FPG, PPG and HbA1c), were repeated and evaluated. Hypoglycemic events were recorded. Tolerability of liraglutide and the dropouts in every schedule visit was assessed.

Statistical methods

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD and results on categorical measurements are presented in Number (%). Significance is assessed at a level of 5%. Unpaired t-test has been used to find the significance of study parameters between the two cohorts on continuous scale. Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two cohorts. Paired t-test was used to find any significant within group changes between baseline and at 24weeks. The following assumptions on data are made.

Assumptions

i. Samples drawn from the population should be

ii. Cases of the samples should be independent

Normality of data was tested by Shapiro-Wilk test, Kolmogorov-Smirnoff and Anderson Darling test. Unpaired t-test has been used to find the significance of study parameters between the two cohorts. Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two cohorts.

Statistical software

The Statistical software namely SAS (Statistical Analysis System, Version 9.2 for windows, SAS Institute Inc., Cary, NC, USA) and SPSS (Statistical Package for the Social Sciences, Version 21.0 for Windows, SPSS, Inc., Chicago, IL, USA) were used for the analysis of the data and Microsoft word and Excel have been used to generate tables.

Results

Cohort A

Thirty two overweight and obese patients with T2D received liraglutide injections between 2010-2012 are considered in cohort A. Mean age of patients was 51.06years (standard deviation±9.53). Mean duration of diabetes was 6.16±2.75years (Table 1). Twenty six patients were followed for 12weeks and 24 patients were followed for 24weeks. Six patients were lost to follow-up before 12weeks and another two patients were lost to follow-up in next 12weeks. Ten patients refused to continue liraglutide after 12weeks and another two patients refused to continue liraglutide after 24weeks because of GI intolerance (nausea, vomiting and diarrhea). Four more patients refused to continue liraglutide beyond 12weeks because of lack of benefit in weight (Table 2). However, no hypoglycemic episodes were reported. Baseline HbA1c (%) was 8.45±1.61 and at 24weeks, HbA1c was non-significantly reduced to 8.22±2.13 (*P* value 0.72). After 24weeks of liraglutide therapy, FPG decreased non-significantly from baseline value of 172.88±67.79 mg/dl to 166.25±85.98mg/dl (*P* value 0.63). After 24weeks of liraglutide therapy, PPG decreased non-significantly from a baseline value of 216.23±80.78mg/dl to 172.11±53.50mg/dl (*P* value 0.99). Baseline weight was 85.42±14.03kg, with a BMI of 34.45±4.85kg/m^2. At 24weeks follow-up, 24 out of 32 patients who continued liraglutide, had a significant weight loss of 3.28kg (*p* value 0.005) and significant decrease in BMI of 0.99kg/m^2(2.87%), (P value 0.008), (Table 3, Figure 1).

Cohort B

Thirty one overweight and obese patients with T2D received liraglutide injections from 2013-2015 are considered in cohort B. Mean age of patients was 48.63±8.92years. Mean duration of diabetes was 8.06±3.38years (Table 1). Twenty nine patients were followed for 12weeks and 25 patients were followed for 24 weeks, as less number of patients was lost to follow up in this cohort. Only one patient was lost to follow-up before 12weeks and another four patients were lost to follow-up in next 12weeks. Only five patients refused to continue liraglutide beyond 12weeks and another two patients refused

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to continue liraglutide beyond 24weeks because of GI intolerance (nausea, vomiting and diarrhea). On further follow-up, one patient beyond 12weeks and three more patients beyond 24weeks refused to continue liraglutide, because of lack of benefit in weight (Table 2). However, no hypoglycemic episodes were reported in this cohort also. Baseline HbA1c (%) was 8.68±2.14 and at 24weeks, HbA1c was non-significantly reduced at 8.27±1.97 (*P* value 0.17). After 24weeks of liraglutide therapy, FPG decreased non-significantly from a baseline value of 175.10±74.04mg/dl to 157.41±65.04mg/dl (*P* value 0.87). After 24 weeks of liraglutide therapy, PPG decreased non-significantly from baseline value of 220.32±97.35mg/dl to 216.30±78.11mg/dl (*P* value 0.23). Baseline weight was 83.13±14.61kg, with a BMI of 34.10±4.32kg/m^2. At 24 weeks follow-up, 25 of out of 31 patients who continued liraglutide, had a significant mean weight loss of 2.05 kg (*p* value 0.0003) and significant mean decrease in BMI of 1.1kg/m^2(3.23%), (*P* value<0.0001), (Table 3).

Table 1 Baseline Characteristics

Variable	Cohort: 2010-12, N=32		Cohort: 2013-15, N=31		p
	Mean	Std. Dev.	Mean	Std. Dev.	
AGE, year	51.06	9.53	48.63	8.92	0.29
Duration of DM, year	6.16	2.75	8.06	3.38	0.18
Height, cm	157.22	9.88	155.81	9.58	0.56
Weight, kg	85.42	14.03	83.13	14.61	0.52
BMI, kg/m^2	34.45	4.85	34.1	4.32	0.75
DBP, mmHg	82.75	11.5	83.35	9.13	0.81
SBP, mmHg	137.69	18.61	131.35	17.77	0.17
FPG, mg/dL	172.88	67.79	175.1	74.04	0.91
PPG, mg/dL	216.23	80.78	220.32	97.35	0.85
HbA1C, %	8.45	1.61	8.68	2.14	0.67

p<0.05 considered as statistically significant, p value computed by unpaired t-test

Table 2 Compliance Profile

	C:2010-12	C:2013-15	p
Total no of patient	32	31	
No of patients studied for 12weeks	26(81.25%)	29(90.63%)	0.74
No of patients studied for 24weeks	24(75%)	25(78.13%)	0.89
Lost to follow-up before 12weeks	6(18.75%)	1(3.23%)	0.104
Lost to follow-up before 24weeks	2(6.25%)	4(12.9%)	0.42
Refused to continue liraglutide after 12weeks because of GI	10(31.25%)	5(16.13%)	0.23
Refused to continue liraglutide after 24weeks because of GI	2(6.25%)	2(6.45%)	1
Refused to continue liraglutide after 12weeks because of no weight loss	4(12.5%)	1(3.23%)	0.35
Refused to continue liraglutide after 24weeks because of no weight loss	0(0%)	3(9.68%)	0.11
No of patients continuing beyond 24weeks	8(25%)	15(48.39%)	0.069
Mean weightloss at 12weeks	2.89	1.62	0.002
Mean weightloss at 24weeks	3.28	2.05	0.005

p<0.05 considered as statistically significant, p value computed by Fischer's exact test for categorical variables and paired t-test for numerical variables

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Table 3 Change in Study Parameters

Cohort	N	Variable	Mean	Std. Dev.	p
2010-12 (Cohort A)	32	Weight-Initial	85.42	14.03	0.005
		Weight-Final	82.14	12.79	
		BMI-Initial	34.45	4.85	0.008
		BMI-Final	33.46	4.01	
		FPG-Initial	172.88	67.79	0.63
		FPG-Final	166.25	85.98	
		PPG-Initial	216.23	80.78	0.99
		PPG-Final	172.11	53.5	
		A1C-Initial	8.45	1.61	0.72
		A1C-Final	8.22	2.13	
2013-15 (Cohort B)	31	Weight-Initial	83.13	14.61	0.0003
		Weight-Final	81.08	11.9	
		BMI-Initial	34.1	4.32	<0.0001
		BMI-Final	33	4.01	
		FPG-Initial	175.1	74.04	0.87
		FPG-Final	157.41	65.05	
		PPG-Initial	220.32	97.35	0.23
		PPG-Final	216.3	78.11	
		HBA1C-Initial	8.68	2.14	0.17
		HBA1C-Final	8.27	1.97	

p<0.05 considered as statistically significant, p value computed by paired t-test, Initial and Final values were captured at baseline and at 24weeks respectively

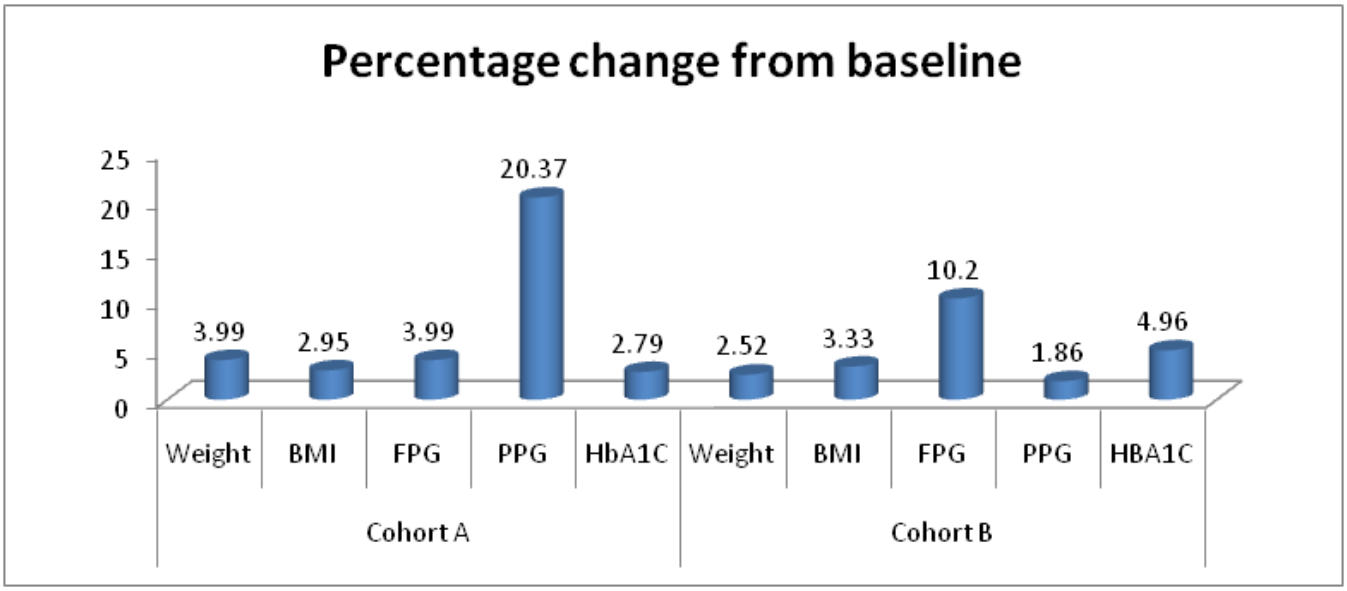

Figure 1 Percentage change in study parameters.

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Discussion

Although American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) guidelines recommend lifestyle and metformin as initial therapy for T2D,[9] sulphonylureas are widely used. Most drugs including sulphonylureas, that target T2D, also cause weight gain or hypoglycemia, or both, with the risk increasing with combination therapy. GLP-1 based therapies, like liraglutide, stimulates insulin secretion, reduces glucagon secretion, slows gastric emptying, reduces appetite and results in weight loss with lesser chances of hypoglycemia.[10] But the cost of therapy and GI intolerance are important impediments to adherence and long-term compliance. In LEAD (Liraglutide Effect and Action in Diabetes) trials, recommended starting dose of liraglutide was 0.6mg daily for at least one week to establish tolerability and then escalating to 1.2-1.8mg daily.[5] GIintolerance of liraglutide were transient and can be alleviated by gradual dose escalation of liraglutide. In the recently published LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial, liraglutide used at a dose of 1.8mg daily (or maximum tolerated dose), the gastrointestinal disorders viz. nausea, vomiting, diarrhea, abdominal pain, abdominal discomfort and decreased appetite were primarily responsible for permanent discontinuation of liraglutide. All of these recorded GI events were significantly higher in liraglutide arm than the matched placebo arm.[11] Nevertheless, in our past experience, a significant proportion of our patients dropped out or refused to continue even low dose (0.6mg) liraglutide because of GI intolerance (which was much higher than LEAD study.[4] To overcome these GI side-effects, liraglutide in 0.2mg per day was used as starting dose and weekly up-titrated to 0.6mg per day, during the last three years (2013-2015) (cohort B). The dose could not be escalated further in our patients, due to prohibiting cost.

Comparing cohort A and cohort B

Baseline characteristics: A total of 63 patients, with 32 in cohort A and 31 in cohort B received liraglutide. There was no statistically significant difference in baseline characteristics namely age, duration of diabetes, height, weight, BMI, DBP, SBP, FPG, PPG and HbA1c between Cohort A and Cohort B (Table 1).

Glycemic control: At 24weeks, the mean reduction from baseline HbA1c was 0.23 percentage points (2.72%) and 0.41 percentage points (4.73%) in cohort A and cohort B respectively. The reduction of HbA1c was not statistically significant in either cohort. The reduction of mean baseline FPG was 6.41mg/dl(3.71%) and 17.69mg/dl(10.1%) in cohort A and cohort B respectively and the reduction in FPG was not statistically significant in either cohort. The reduction of mean baseline PPG was 45.12mg/dl(20.87%) and 4.02mg/dl(1.82%) in cohort A and cohort B respectively, but again the reduction in PPG in either cohort was not statistically significant. Hence, no significant changes were observed in glycemic parameters after 24weeks of liraglutide therapy either starting with a dose of 0.6mg in cohort A or with 0.2 mg in cohort B. Table 3 However, as the data were captured from real world out-patient clinic, regular adjustment of other anti-diabetic medications based on prevailing clinical situations, cannot be ruled out and may be responsible for poor glycemic improvement in our patients. In LEAD-2 trial, reductions in HbA1c (1%) was achieved only with the higher doses of liraglutide (1.2 and 1.8mg) and the HbA1C decrease was 0.7% for 0.6mg liraglutide.[5] Kesavadev *et al.*[12] evaluated the efficacy and safety of 1.8mg/day liraglutide in 14 overweight and obese Indian T2D patients (diabetes <12weeks). Mean HbA1c (2.26%) and weight (8.65kg) reduction was greater than LEAD studies.[12] On the other hand, in recently published LEADER trial, HbA1c was lowered only by 0.4% at three years.[7] In the present retrospective study in a real-life setting, low dose liraglutide (0.6mg/day) reduced HbA1c by 0.23% and 0.41% in cohort A and cohort B respectively. There were no episodes of hypoglycemia reported in either of the cohorts.

Weight reduction: In contrary to glycemic control, weight reduction was significant in both cohorts after 24weeks of liraglutide therapy. A statistically significant 3.28kg(3.84%) and 2.05kg(2.47%) mean weight reduction were observed in cohort A and cohort B respectively. Although mean weight loss at 12weeks and 24weeks follow-up visits were statistically significant in both the cohorts, the absolute weight loss in cohort A was better (3.28kg) compared to cohort B (2.05kg). The relative weight reduction from baseline level was higher in cohort A (3.84%) than cohort B (2.47%) (Table 2), probably because of higher GI intolerance in cohort A. In LEAD-2, weight loss was dose dependent: 1.8±0.2, 2.6±0.2 and 2.8±0.2kg for 0.6mg, 1.2mg and 1.8mg liraglutide, respectively. The GI intolerance in LEAD-2 was also dose dependent: 35%, 40% and 44% with 0.6, 1.2 and 1.8mg liraglutide, respectively.[5] Though the absolute and relative weight reduction was higher in the cohort A than cohort B (Table 2), it is worth mentioning that both absolute and relative reduction in BMI was numerically higher in Cohort B (1.10kg/m^2) than Cohort A (0.99kg/m^2) (Table 3). The reduction in body weight and BMI are both in the range of statistical significance, however p values associated with reduction in cohort B suggests a lower element of chance, thereby implying stronger significance.

Benefit of 0.2mg starting dose: Though statistically not superior, cohort B scored over cohort A with respect to change in BMI and tolerability (the number of patients continuing liraglutide beyond 12weeks and 24weeks) with similar efficacy in glycemic control. For the number of patients continuing liraglutide beyond 24weeks ($p=0.069$), falls in the range of suggestive significance (p value: $0.05<p<0.10$), which reveals a trend in the data.[11] The chance element is more than five per cent but less than ten percent and provides suggestive evidence against the null hypothesis of equal proportion in both cohorts. Also from our present study experience, we recall most of the patients in the cohort A dropping out early owing to GI intolerance compared to cohort B in both the 12weeks and 24weeks follow up, accounting for a substantial differential follow-up bias. Had we accounted for the exact number of days the patients being on liraglutide therapy, we might have reached a different conclusion? Nevertheless, being a real world scenario we couldn't address the problem. A properly planned and well-designed study might address all the above mentioned issues. One of the major limitations for not demonstrating statistically significant benefit in cohort B with respect to cohort A, might be due to the small sample size of the study. An adequately powered study with a power of 80% or higher along with a significance level set at 5% would warrant around 73 subjects in each cohort as computed with the help of a reputed sample size estimation software PS™ (based on the data generated from the present study).

Conclusion

Liraglutide once a day non-significantly improved glycemic control and significantly decreased weight and BMI, in obese and overweight uncontrolled longstanding T2D. However, a significant proportion of

patients dropped out because of GI intolerance. Starting with a very low dose (0.2mg) liraglutide and weekly up-titration appears better tolerated (though not statistically significant). An adequately powered prospective study is required to establish the benefit of 0.2mg starting dose in minimization of GI intolerance.

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Conflict of interest

Author declares that there is no conflict of interest.

References

1. Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev.* 2007;87:1409–1439.
2. Knudsen LB, Nielsen PF, Huusfeldt PO, et al. Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. *J Med Chem*. 2000;43:1664–1669.
3. Agerso H, Jensen LB, Elbrond B, et al. The pharmacokinetics, pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1 derivative, in healthy men. *Diabetologia*. 2002;45:195–202.
4. Sanyal D, Majumdar A. Low dose liraglutide in Indianpatients with type 2 diabetes in the real world setting. *Indian J EndocrMetab.* 2013;17:301–303.
5. Nauck M, Frid A, Hermansen K, et al. 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.
6. Ramachandran A. Diabetes & obesity - The Indian angle. *Indian J Med Res*. 2004;120:437–439.
7. Marso SP, Daniels GH, Frandsen KB, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2016;375(4):311–322.
8. Gross B. Clinical pearls for initiating and utilizing liraglutide in patients with type 2 diabetes. *J Pharm Pract*. 2013;26(2):144–150.
9. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2015;38(1):140–149.
10. Madsbad S. Liraglutide effect and action in diabetes (LEAD) trial. *Expert Rev Endocrinol Metab*. 2009;4:119–129.
11. Cummings P, Rivara FP. Reporting statistical information in medical journal articles. *Arch Pediatr Adolesc Med.* 2003;157(4):321–324.
12. Kesavadev J, Shankar A, Krishnan G, et al. Liraglutide therapy beyond glycemic control: An observational study in Indian patients with type 2 diabetes in real world setting. *Int J Gen Med*. 2012;5:317–322.