Liraglutide – Indian Experience

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Abstract

Liraglutide is an effective drug for the treatment of type 2 diabetes mellitus (T2DM). The aim of this review is to collate evidence on the real-world clinical effectiveness of liraglutide from the published Indian studies. A review of publications was conducted to identify observational studies that assessed the effectiveness of liraglutide among Indian T2DM. Total ten publications were retrieved and these observational studies are compared with the results of the liraglutide randomized controlled trial (RCT) program (Liraglutide Effect and Action in Diabetes [LEAD]). Liraglutide therapy demonstrated HbA1c reduction in the Indian population up to 2.26% and 2.54%, over 24 and 52 weeks, respectively. Among the LEAD trials, the HbA1c reduction at 24 weeks was maximum in LEAD-4 with 1.5% reduction at both doses used (1.2 and 1.8 mg) and up to 1.14% in LEAD-3 with a dose of 1.8 mg. The weight loss among Indian subjects was generally around 5 kg or more with maximum weight loss of 8.6 kg over 24 weeks. The maximal weight loss in LEAD studies was less than 3 kg with an exception of 3.24 kg in LEAD-6. In over 52 weeks of liraglutide therapy among Indian subjects, mean weight loss was 7.4 kg, which was 3.5 times more than of LEAD program. Two Indian observational studies also demonstrated significant weight loss among nondiabetic obese subjects at a much lower than that of 3 mg anti-obesity dose. Gastrointestinal (GI) events are the commonly reported adverse events with Indian studies as well as LEAD program. Liraglutide therapy produces better glycemic control and more weight loss among Indian T2DM subjects compared with RCTs conducted in western population with almost similar adverse consequences.

Keywords: Effectiveness, India, liraglutide, literature review, real-world, type 2 diabetes, weight

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RA) are being recognized as an important therapeutic option in the management of type 2 diabetes mellitus (T2DM). Liraglutide is a unique GLP-1RA with 97% homology to endogenous human GLP-1 and a commonly prescribed anti-diabetic agent. In liraglutide, at the 34th position arginine has been replaced with lysine and a C-16 palmitic acid side chain has been attached to the lysine at the 26th position. The modifications in the structure lead to slow absorption from the subcutaneous tissue, resistance to degradation by endogenous dipeptidyl peptidase-4 (DPP4) enzyme and reversible albumin binding. This prolongs the half-life of liraglutide to 13 hours, enabling once daily administration.[1,2]

Liraglutide was first approved for treatment of T2DM as an adjunct to lifestyle therapy and in combination with oral anti-diabetic drugs (OADs) in Europe in 2009 and in the United States in 2010.[3] It was approved for use in India in 2010. The approval of liraglutide was based on the outcomes from the Liraglutide Effect and Action in Diabetes (LEAD) phase 3 clinical trial program, which showed the anti-hyperglycemic efficacy of liraglutide in T2DM both as monotherapy and when combined with other glucose lowering anti-diabetic medications.[4-9]

Results from randomized controlled trials (RCTs) are obtained under supervised conditions and the clinical effects of the drugs may vary depending on a lot of practical factors. Although cost is a limiting factor for prolonged use of this drug in our country, there has been significant interest among Indian clinicians, as evidenced by recent publications. Ten observational studies have recently been published with liraglutide in a real-world setting (Jothydev *et al.*, Kaur *et al.*, Sanyal *et al.*, Roy Chaudhri *et al.*, Wagnoo *et al.*, Verma *et al.*, and Majumder *et al.*), from

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various parts of India.[10-19] We are presenting a review of the real-world experience with liraglutide in India.

METHODS

This literature review was conducted to collect evidence on the effectiveness and adverse effects of liraglutide, from the real-world studies in India. The PubMed database and Index Copernicus were searched. In the database search, no time limits were applied to ensure that no relevant publications were missed. Total ten publications were retrieved from the search evaluating the glycemic efficacy, weight loss, and adverse effect parameters in observational studies. Out of these, seven were on T2DM, two on obesity, and one evaluating the impact of starting very low dose on adverse parameters. The database search was executed on January 7, 2018. These seven observational studies on T2DM are compared with the results of the LEAD program.

Characteristics of study design

Indian observational studies with liraglutide had evaluated the efficacy (glycemic parameters and weight loss) and adverse consequences. Pertinent study design of these observations and LEAD program (a series of six-phase three RCTs) are presented in Tables 1 and 2.

Patient baseline characteristics

Number of subjects in all Indian observational studies with liraglutide was small compared with LEAD program, which comprised more than 4,000 patients. The mean age of patients with Indian T2DM on liraglutide was between 43.64 and 55.9 years at baseline. Three out of seven publications included more male than female subjects. The mean baseline HbA1c level before liraglutide treatment was between 7.78% and 9.08%. Mean baseline weight and mean baseline body mass index (BMI) were 85.71–98.9 kg/m^2 and 33.22–36.2 kg/m^2, respectively. Differences were observed in the baseline characteristics, especially regarding use of

concomitant and previous anti-diabetic therapy and the information on the use of prior therapies varied between the studies. The baseline characteristics of patients of Indian studies and the LEAD program are presented in Tables 3 and 4.

Clinical effectiveness

The clinical effectiveness of anti-diabetic drugs on blood glucose control is measured by HbA1c, fasting plasma glucose (FPG), and post-prandial plasma glucose (PPG). The change in mean FPG, PPG, and HbA1c from baseline to end of study of both the Indian studies and LEAD program are shown in Tables 5 and 6.

Change in body weight

Reduction in body weight is associated with reduced risk of developing cardiovascular disease in obese patients with diabetes. Overall, liraglutide treatment both as monotherapy and in combination with oral therapy led to significant weight loss in patients with T2DM. Body weight reduction ranged from 1.18 to 8.65 kg in Indian subjects, whereas the LEAD program has reported a weight gain of 0.3 kg to a loss of 3.24 kg, as shown in Tables 7 and 8.

DISCUSSION

The LEAD trial program consisted of a series of six phase-3 RCTs that was conducted at more than 600 sites, across 40 countries, comprising more than 4,000 patients, out of which around 2,700 patients received liraglutide therapy.[4-9] All the LEAD trials were of 26 weeks duration with the sole exception of LEAD-3, which was a 52-week study.

Among the studies of liraglutide reported from India, three initial studies reported by Kesavadev *et al.* (2012),[10] Sanyal *et al.* (2013),[18] and Kesavadev *et al.* (2014)[14] were for a period of 24 weeks. However, as time progressed, it became relatively easier for the clinicians to gather data of subjects continuing liraglutide for a year and more. There were two publications from Kaur *et al.* (2016)[12] and Roy Chaudhuri *et al.* (2016)[15]

Table 1: Study design of Indian studies and LEAD				
	Study design	Sample size	Study duration	Region
Kesavadev *et al.* (2012)	Single-center, prospective, open-labeled, single-arm, observational study	14	24 weeks	Trivandrum, Kerala
Sanyal *et al.* (2013)	A single-center, retrospective observational study	30	24 weeks	Kolkata, West Bengal
Kesavadev *et al.* (2014)	Prospective, open-labeled, single-arm, single-center, observational study	195	24 weeks	Trivandrum, Kerala
Kaur *et al.* (2014)	Single-center, prospective, open-labeled, single-arm, observational study	196	13 weeks	Gurgaon, Haryana
Kaur *et al.* (2016)	Single-center, prospective, open-labeled, single-arm, observational study	96	52 weeks	Gurgaon, Haryana
Wagnoo *et al.* (2016)	Open-label prospective observational study	1,416	26 weeks	125 sites across India
Chaudhuri *et al.* (2016)	Single-center, retrospective, real-world, observational study	39	82 weeks	Kolkata, West Bengal
LEAD trials	RCT, prospective, active comparator, double blind	2739	(LEAD-1,2,4-6)-26 weeks LEAD 3-52 weeks	600 sites across 40 countries

LEAD: Liraglutide effect and action in diabetes; RCT: Randomized controlled trial

Table 2: Overview of the design of the LEAD studies individually

Study	Study characteristics	Study treatment	Comparator	Combination treatment
LEAD-1	26-week double-blind, double-dummy, randomized, placebo-, and active-controlled, parallel-group study Patients with type 2 diabetes who previously received ≥1 OAD	Liraglutide: 0.6 mg Liraglutide: 1.2 mg Liraglutide: 1.8 mg	Rosiglitazone: 4 mg Placebo	Glimepiride: 2-4 mg/day
LEAD-2	26-week double-blind, double-dummy, randomized, placebo, and active-controlled, parallel-group study Patients with type 2 diabetes who previously received ≥1 OAD	Liraglutide: 0.6 mg Liraglutide: 1.2 mg Liraglutide: 1.8 mg	Glimepiride: 4 mg Placebo	Metformin: 1 g BID
LEAD-3	52-week double-blind, double-dummy, randomized, active-controlled, parallel-group study Patients with type 2 diabetes who were previously on diet/exercise or received OAD	Liraglutide: 1.2 mg Liraglutide 1.8 mg	Glimepiride: 8 mg	-
LEAD-4	26-week double-blind, randomized, placebo-controlled, parallel-group study Patients with type 2 diabetes who previously received ≥1 OAD	Liraglutide: 1.2 mg Liraglutide: 1.8 mg	Placebo	Metformin: 1 g BID Rosiglitazone: 4 mg BID
LEAD-5	26-week randomized, placebo-controlled, parallel-group study Patients with type 2 diabetes who previously received ≥1 OAD	Liraglutide: 1.8 mg	Insulin glargine: 24 IU/day	Metformin: 1 g BID Glimepiride: 4 mg/day
LEAD-6	26-week open-label, randomized, active-controlled, parallel-group study Patients with type 2 diabetes who previously received metformin and/or SU	Liraglutide: 1.8 mg	Exenatide: 10 µg BID	Metformin and/or SU (pre-trial OAD treatment regimen was maintained)

LEAD: Liraglutide effect and action in diabetes, OAD: Oral anti-diabetic drug

Table 3: Baseline characteristics of Indian studies and LEAD

	Jothydev *et al*. (2012)	Sanyal *et al*. (2013)	Jothydev *et al*. (2014)	Kaur *et al*. (2014)	Kaur *et al*. (2016)	Chaudhuri *et al*. (2016)	Wagnoo *et al*. (2016)	LEAD trials	
								Lira 1.8 mg	Lira 1.2 mg
No. of patients	14	30	195	196	96	39	1416	1581	1117
Male:female	1:1	3.2:1	1.2:1	-	1.6:1	0.7:1	1.33:1	1.1:1	1:1
Age (years, mean±SD)	43.64±13.89	50.5	45.87±10.71	49.9±9.6	50.9±9.6	47.89±11	46.8±9.7	55.5	55.9
Duration of T2DM (week, mean±SD)	33.50±80.28	5.8±3.97	6.48±6.35	7.5±4.5	11.6±6.3	6.46±4.55	7.2±5.6	30.33±10.61	32.5±13
HbA1c (%)	7.78±1.74	8.03±1.49	8.14±1.89	9.2±1.9	8.9±1.3	9.08±1.54	8.8±1.3	8.4	8.4
Fasting plasma glucose (mg/dL)	147.57±46.68	168.3±21.5	163.81±67.47	173.7±6.3	181.2±77.1	200.82±53.73	70.6±47.8		
Postprandial plasma glucose (mg/dL)	167.57±77.44	210.5±69.4	-	252.5±77.0	229.1±81.6	261.08±75.84	251.4±68.0		
Weight (kg, mean±SD)	90.71±11.80	85.71±14.47	86.40±12.82	100.1±17.5	98.9±16.0	88.27±10.68	92.5±14.6	90.1	89.7
Body mass index (kg/m^2, mean±SD)	33.49±5.15	34.6±5.08	-	36.2±5.4	-	33.22±4.51	34.4±5.5	31.9	31.9

LEAD: Liraglutide effect and action in diabetes, T2DM: Type 2 diabetes mellitus

that looked at results of 52 weeks and more. Despite these latter two publications being of a longer duration, data at 26 weeks and 52 weeks were also available for analysis for this review.

Glycemic control parameters: Plasma glucose and HbA1c

In the LEAD trials, when used as monotherapy, liraglutide showed significant improvements in the glycemic parameters compared with glimepiride and also when used in combination with one or two OADs. LEAD-1, LEAD-2, and LEAD-4 evaluated both doses of liraglutide (viz., 1.2 mg and 1.8 mg per day). LEAD-4 and LEAD-2 reported 1.5% and 1% reduction in HbA1c, respectively, which was similar at both the doses. A numerically improved HbA1c reduction of 1.13% with 1.8 mg dose versus a reduction of 1.08% with 1.2 mg dose was seen in LEAD-1. However, this marginal difference was not clinically significant and in real

Table 4: Patient demographics and baseline characteristics of LEAD studies individually (Adapted from Davies *et al.*)

Study	Arm	Patients (*n*)	Age (years)	Gender (M/F), %	Weight (kg)	BMI (kg/m^2)	Duration of diabetes (years)	HBA1c (%)	FPG (mg/dL)
LEAD-1	Liraglutide: 1.2 mg	228	57.7 (9.0)	45/55	80.0 (17.1)	29.8 (5.1)	6.7 (4.0, 10.7)	8.5 (1.1)	176.4
	Liraglutide: 1.8 mg	234	55.6 (10.0)	53/47	83.0 (18.1)	30.0 (5.1)	6.5 (3.7, 10.5)	8.5 (0.9)	174.6
LEAD-2	Liraglutide: 1.2 mg	241	57 (9)	54/46	88.5 (19.1)	31.1 (4.8)	7 (5)	8.3 (1.0)	178.2
	Liraglutide: 1.8 mg	242	57 (9)	59/41	88.0 (16.3)	30.9 (4.6)	8 (5)	8.4 (1.0)	180.1
LEAD-3	Liraglutide: 1.2 mg	251	53.7 (11.0)	47/53	92.5 (19.2)	33.2 (5.6)	5.2 (5.5)	8.3 (1.0)	167.4
	Liraglutide: 1.8 mg	247	52.0 (10.8)	49/51	92.8 (20.7)	32.8 (6.3)	5.3 (5.1)	8.3 (1.1)	172.47
LEAD-4	Liraglutide: 1.2 mg	178	55 (10)	57/43	95.5 (18.5)	33.2 (5.4)	9 (6)	8.5 (1.2)	180.1
	Liraglutide: 1.8 mg	178	55 (11)	51/49	94.9 (19.2)	33.5 (5.1)	9 (6)	8.6 (1.2)	185.4
LEAD-5	Liraglutide: 1.8 mg	232	57.6 (9.5)	57/43	85.5 (19.4)	30.4 (5.3)	9.2 (5.8)	8.3 (0.9)	163.8
LEAD-6	Liraglutide: 1.8 mg	233	56.3 (9.8)	49/51	93·1 (20.1)	32.9 (5.5)	8.5 (6.2)	8.2 (1.0)	176.4

LEAD: Liraglutide effect and action in diabetes, BMI: Body mass index, FPG: Fasting plasma glucose

Table 5: Change in glycemic parameters of Indian studies

	Baseline	At the end of study	Mean change	*P*
Kesavadev *et al*. (2012)-24-week study				
HbA1c (%)	7.78±1.74	5.52±0.53	−2.26	<0.001
FPG (mg/dL)	147.57±46.68	99.07±22.55	−48.5	0.002
PPG (mg/dL)	167.57±77.44	100.86±35.72	−66.71	0.004
Sanyal *et al*. (2013)-24-week study				
HbA1c (%)	8.03±1.49	7.29±0.94	−0.74	<0.05
FPG (mg/dL)	168.3±21.5	129.8	−38.5	<0.05
PPG (mg/dL)	210.5±69.4	159.29	−50.71	<0.05
Kesavadev *et al*. (2014)-24-week study				
HbA1c (%)	8.14±1.89	6.96±1.16	−1.18	0.006
FPG (mg/dL)	163.81±67.47	111.60±30.61	−52.21	<0.001
PPG (mg/dL)	-	-	-	-
Kaur *et al*. (2014)-13-week study				
HbA1c (%)	9.2±1.9	7.6±0.99	−1.6	0.007
FPG (mg/dL)	173.7±6.3	115.5±25.1	−58.2	0.005
PPG (mg/dL)	252.5±77.0	177.1±31.2	−75.4	0.002
Kaur *et al*. (2016)-52-week study				
HbA1c (%)	8.9±1.3	7.4±1.2	−1.4	<0.01
FPG (mg/dL)	181.2±77.1	128.5±39.7	−52.7	<0.05
PPG (mg/dL)	229.1±81.6	181.8±47.3	−47.3	<0.05
Chaudhuri *et al*. (2016)-82-week study				
HbA1c (%)	9.08±1.54	7.26±1.02	−2.54	<0.0001
FPG (mg/dL)	200.82±53.73	135.27±49.8	−65.55	<0.001
PPG (mg/dL)	261.08±75.84	177.67±63.66	−83.41	<0.001
Wagnoo *et al*. (2016)-26-week study				
HbA1c (%)	8.8±1.3	7.2±0.8	−1.6±1.1	<0.0001
FPG (mg/dL)	170.6±47.8	139.9±34.4	−44.0±39.7	<0.0001
PPG (mg/dL)	251.4±68.0	90.7±41.9	−80.0±57.5	<0.0001

FPG: Fasting plasma glucose, PPG: Post-prandial plasma glucose

The first Indian publication by Jothydev *et al.* (2012)[10] reported the most spectacular reduction of HbA1c up to 2.26% over 24 weeks. However, the numbers of subjects included were only 14 and the dose of liraglutide used was 1.8 mg/day, which was not always the dose majorly used in the rest of the Indian studies. In contrast, Sanyal *et al.* (2013)[18] published the results of low-dose liraglutide (0.6 mg) over 24 weeks, demonstrating a much lesser drop of HbA1c (0.74%). However, the other two Indian data showed a robust reduction of HbA1c with Kaur *et al.* (2016)[12] reporting a reduction of 1.4% and Roy Chaudhuri *et al.* (2016)[15] reporting a reduction of 2.54% using varying doses of liraglutide between 0.6 mg and 1.8 mg per day. An overview of the changes in the mean HbA1c level achieved in 24 and 52 weeks by liraglutide treatment in Indian studies compared with the LEAD program is given in Figure 1 (Panel A).

With regard to the FPG reduction at 24 weeks, LEAD-4, which used rosiglitazone and metformin as concomitant medication, showed the most robust reduction of 39.6 mg/dL with 1.2 mg dose and 43.2 mg/dL with 1.8 mg dose. On the other hand, the Indian data showed a reduction of 38.5 mg/dL with low dose of liraglutide (0.6 mg) (Sanyal *et al.* 2013)[18] and a more robust reduction of 48.5 mg/dL (Kesavadev *et al.* 2012)[10] to 58.2 mg/dL (Kaur *et al.* 2016)[12] with higher doses. At 1-year mark, LEAD-4 showed a reduction of FPG of 15.12 mg/dL and 25.56 mg/dL with 1.2 and 1.8 mg doses, respectively. However, the other two available Indian data of a duration of 52 weeks or more reported a robust reduction of 52.7 mg/dL (Kaur *et al.* 2016)[12] and 59.65 mg/dL (Roy Chaudhuri *et al.*, 2016).[15] An overview of the changes in the mean FPG level achieved in 24 and 52 weeks by liraglutide treatment in Indian studies compared with the LEAD program is given in Figure 1 (Panel B).

PPG is important in the Indian subset as they have a predominantly carbohydrate-based diet. Indian observational data suggested a better reduction with liraglutide compared with the LEAD program. LEAD-5 produced the least reduction of 32.4 mg/dL at 24 weeks using a dose of 1.8 mg, while LEAD-6 achieved a maximum reduction of

life involves an extra financial burden which is a concern in poor-resource settings, especially in India, which is majorly an out-of-pocket market. In LEAD-3, over 52 weeks, 1.8 mg dose achieved a reduction of 1.14% in HbA1c versus 0.84% with 1.2 mg dose.

Table 6: Change in glycemic parameters in LEAD trials individually

Liraglutide dose	Baseline		At the end of study		Mean change		*P*	
	1.2 mg	1.8 mg	1.2 mg	1.8 mg	1.2 mg	1.8 mg	1.2 mg	1.8 mg
LEAD 1								
HbA1c (%)	8.5	8.5	7.42	7.37	−1.08	−1.13	<0.0001	<0.0001
FPG (mg/dL)	176.4	174.6	146.14	145.98	−28.26	−28.62	<0.05	<0.05
PPG (mg/dL)	232.2	232.2	187.20	183.60	−45	−48.6	<0.05	<0.005
LEAD 2								
HbA1c (%)	8.3	8.4	7.3	7.4	−1.00	−1.00	<0.0001	<0.0001
FPG (mg/dL)	178.2	181.8	149.40	151.20	−28.8	−30.6	<0.05	<0.05
PPG (mg/dL)	214.2	219.6	172.80	172.80	−41.4	−46.8	NS	NS
LEAD 3								
HbA1c (%)	8.3	8.3	7.46	7.16	−0.84	−1.14	<0.05	<0.0001
FPG (mg/dL)	167.4	171	152.28	145.44	−15.12	−25.56	<0.05	<0.0001
PPG (mg/dL)	203.4	205.2	172.80	167.40	−30.6	−37.8	NS	<0.005
LEAD 4								
HbA1c (%)	8.5	8.6	7.0	7.1	−1.5	−1.5	<0.0001	<0.0001
FPG (mg/dL)	181.8	185.4	142.20	142.20	−39.6	−43.2	<0.0001	<0.0001
PPG (mg/dL)	205.2	212.4	158.40	163.80	−46.8	−48.6	<0.0001	<0.0001
Liraglutide dose	1.8 mg		1.8 mg		1.8 mg		1.8 mg	
LEAD 5								
HbA1c (%)	8.3		6.97		−1.33		<0.0001	
FPG (mg/dL)	163.8		135.9		−27.9		<0.0001	
PPG (mg/dL)	201.6		169.20		−32.4		NS	
LEAD 6								
HbA1c (%)	8.2		7.08		−1.12		<0.0001	
FPG (mg/dL)	176.4		147.42		−28.98		<0.0001	
PPG (mg/dL)	171		100.80		−70.2		<0.001	

LEAD: Liraglutide effect and action in diabetes, FPG: Fasting plasma glucose, PPG: Post-prandial plasma glucose

Table 7: Change in body weight in Indian studies

	Baseline	At the end of study	Mean change	*P*
Kesavadev *et al*. (2012)-24-week study				
Body weight (kg)	90.71±11.80	82.06±12.86	−8.65	<0.001
Kesavadev *et al*. (2014)-24-week study				
Body weight (kg)	86.41±12.83	82.37±12.45	−1.18	<0.001
Sanyal *et al*. (2013)-24-week study				
Body weight (kg)	85.71±14.47	79.68	−6.03	<0.05
Kaur *et al*. (2014)-13-week study				
Body weight (kg)	100.1±17.5	96±16.5	−4.1	<0.001
Kaur *et al*. (2016)-52-week study				
Body weight (kg)	98.9±16.0	93.8±15.0	−5.1	<0.05
Chaudhuri *et al*. (2016)-82-week study				
Body weight (kg)	88.27±10.68	80.8±11.83	−7.25	<0.0001
Wagnoo *et al*. (2016)-26-week study				
Body weight (kg)	92.5±14.6	84.8±12.9	−8.1	<0.0001

reduction of 50.7 mg/dL (Sanyal *et al*. 2013)[18] at a low dose of 0.6 mg and a maximum reduction of 75.4 mg/dL at a dose of 1.2–1.8 mg (Kaur *et al*. 2016).[12] The 52-week studies also showed a similar trend whereby a reduction of 76.08 mg/dL and 47.3 mg/dL were reported by Roy Chaudhuri *et al*. (2016)[15] and Kaur *et al*. (2016),[12] respectively, whereas the two arms of LEAD-3 reported a PPG reduction of 30.6 mg/dL (with 1.2 mg dose) and 37.8 mg/dL (with 1.8 mg dose). An overview of the changes in the mean PPG level achieved in 24 and 52 weeks by liraglutide treatment in Indian studies compared with LEAD is given in Figure 1 (Panel C).

This accumulated Indian data now tend to suggest that liraglutide is effective in reducing all parameters of glycemic control over a period of 24 weeks and also in the long run, over a year or more, which is more than that of the LEAD program and at times with lower doses also.

Effect of liraglutide on weight and body mass index in diabetic patients

The vast majority of Indian subjects with T2DM are overweight or obese and the impact on weight should be considered while choosing the most appropriate glucose-lowering therapy for these subjects. In addition

70.2 mg/dL with the same dose. Other LEAD trials showed a PPG reduction ranging from 41.4 mg/dL to 48.6 mg/dL. The Indian studies, on the other hand, showed a minimum

Table 8: Change in body weight in LEAD trials individually

Liraglutide dose	Baseline		At the end of study		Mean change		P	
	1.2 mg	1.8 mg	1.2 mg	1.8 mg	1.2 mg	1.8 mg	1.2 mg	1.8 mg
LEAD 1								
Body weight (kg)	80	83	80.3	82.8	+0.3	−0.2	<0.0001	<0.0001
LEAD 2								
Body weight (kg)	88.5	88	85.9	85.2	−2.6	−2.8	<0.0001	<0.0001
LEAD 3								
Body weight (kg)	92.5	92.8	90.4	90.3	−2.1	−2.5	<0.0001	<0.0001
LEAD 4								
Body weight (kg)	95.5	94.9	94.5	92.9	−1.0	−2.0	<0.0001	<0.0001
Liraglutide dose	1.8 mg		1.8 mg		1.8 mg		1.8 mg	
LEAD 5								
Body weight (kg)	85.5		83.7		−1.8		<0.0001	
LEAD 6								
Body weight (kg)	93.1		89.9		−3.24		NS	

LEAD: Liraglutide effect and action in diabetes
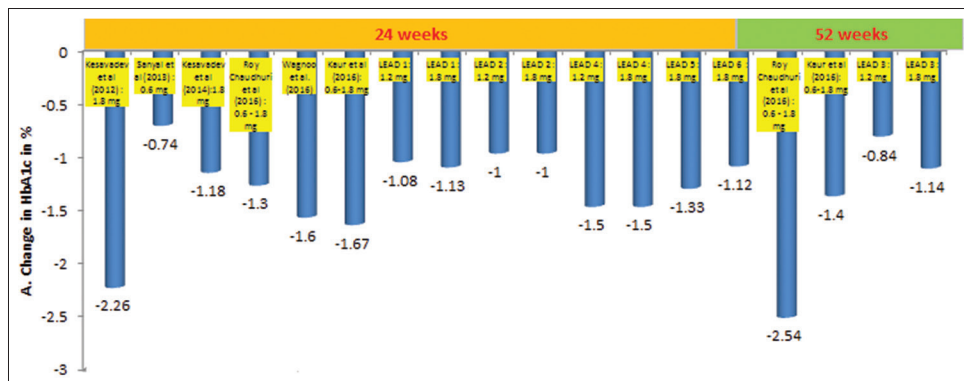
Figure 1 (Panel A): Changes in HbA1c in 24 and 52 weeks by liraglutide treatment in Indian studies compared with LEAD
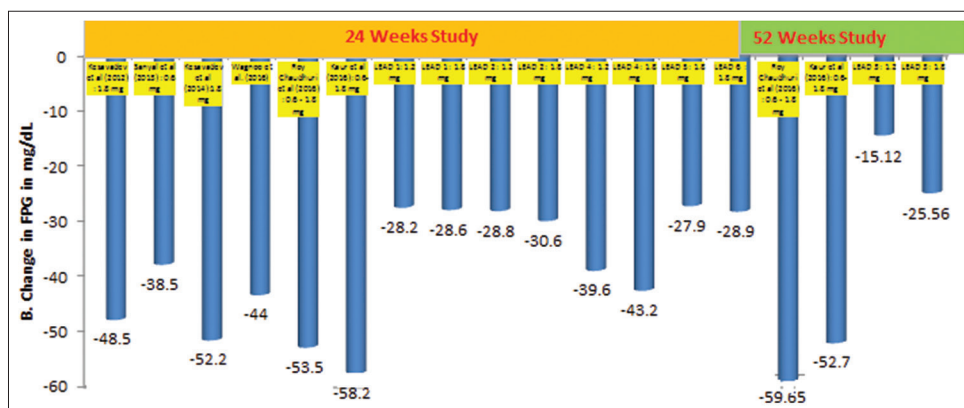
Figure 1 (Panel B): Changes in FPG in 24 and 52 weeks by liraglutide treatment in Indian studies compared with LEAD

to providing significant glycemic control in LEAD studies, liraglutide reduced weight in most subjects. The maximal weight loss in the LEAD program was less than 3 kg, except in LEAD-6 which showed a weight loss of 3.24 kg over a 24-week period. In contrast, the 1.2 mg arm of LEAD-1 (used in addition to glimepiride 2–4 mg) showed a marginal (300 g) increase of weight over a period of 24 weeks. All Indian studies have reported a whopping weight loss in comparison to the LEAD program. The weight loss among Indian subjects (except for one study showing a weight loss of 1.1 kg over 24 weeks by Kesavadev *et al.*, 2014)[14] was generally around 5 kg or

more with the maximum weight loss being reported of 8.6 kg over 24 weeks in a cohort of 14 overweight and obese T2DM subjects (Kesavadev *et al*. 2012).[10] In the long run (over 52 weeks or more), a weight loss of 7.4 kg was about 3.5 times higher than the weight loss reported in LEAD-3 (−2.1 kg and −2.5 kg with 1.2 mg and 1.8 mg, respectively) (Roy Chaudhuri *et al*. 2016).[15]

An overview of the changes in the mean weight achieved in 24 and 52 weeks by liraglutide treatment in Indian studies compared with LEAD is given in Figure 1 (Panel D).

Effect of liraglutide on weight and body mass index in nondiabetic patients

Liraglutide has been shown to be effective at inducing and sustaining weight loss among obese patients, and a 3-mg dose has been approved for chronic weight management in patients with obesity or who are overweight with a BMI ≥ 27 kg/m^2 and have a weight-related co-morbid condition.[21]

Results from Indian observational studies also repeatedly demonstrated the ability of liraglutide to induce weight loss. A weight loss of 8 kg (±2.4 kg) from a baseline weight of 110 kg (±12.5 kg), and waist circumference reduction of 3.1 cm (±1.2 cm) from a baseline waist circumferences of 114 cm (±8.1 cm) was observed among 25 obese non-diabetic

subjects after 12 weeks of liraglutide therapy, with a dose of 1.2 mg (Verma, 2012).[17] Significant reduction of mean body weight (from 96.33 ± 14.45 at baseline to 90 ± 13.47 at 3 months and to 86.25 ± 13.19 at 9 months, $P < 0.001$), BMI (from 34.99 ± 5.66 at baseline to 32.66 ± 5.17 at 3 months to 31.29 ± 4.97 at 9 months, $P < 0.001$), and waist circumference (from 93.33 ± 5.43 at baseline to 90.33 ± 5.09 at 3 months to 88.5 ± 4.59 at 9 months, $P < 0.001$) were reported after 3 and 9 months of liraglutide treatment, with a dose of 1.8 mg (Roy *et al*. 2016).[16] Even a low dose (0.6 mg) of liraglutide showed a reduction of 6.03 kg over 24 weeks. Hence, in the scanty Indian data available, liraglutide at a dose much lower than that of 3 mg (as the approved anti-obesity dose) produced a substantial reduction in body weight of obese non-diabetic Indian subjects, which can make it a relatively less expensive anti-obesity agent in days to come.

Side effect profile

The LEAD program has demonstrated that liraglutide therapy is generally well tolerated, and the most commonly reported adverse event was nausea (7-40%) which was transient and subsided as the treatment progressed.[4-9] Nausea was also a common adverse event in the Indian studies and reported incidences varies from 0.7%[11] to 42.58%.[10]
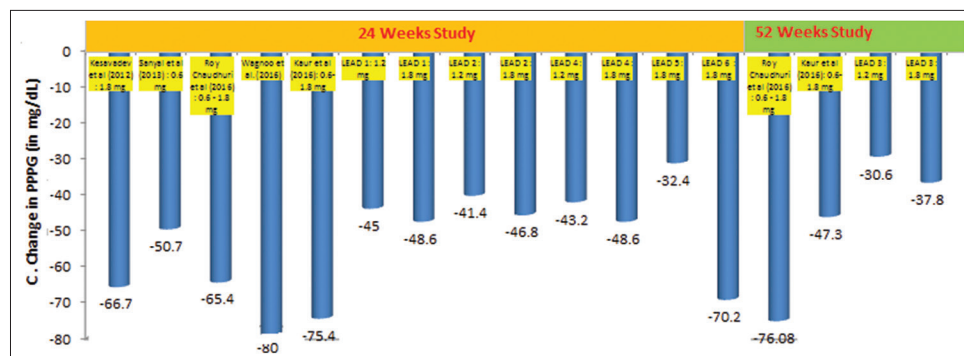

Figure 1 (Panel C): Changes in PPPG in 24 and 52 weeks by liraglutide treatment in Indian studies compared with LEAD
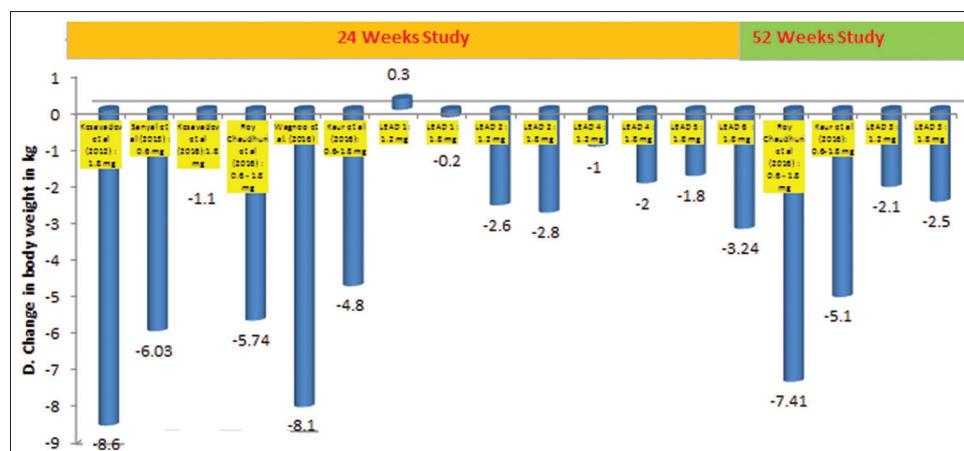

Figure 1 (Panel D): Changes in body weight in 24 and 52 weeks by liraglutide treatment in Indian studies compared with LEAD

Vomiting, diarrhea, dyspepsia, and constipation are the other adverse events reported in the LEAD program and the cumulative gastrointestinal (GI) adverse events ranged up to 54% in these trials.[5] The GI events were often dose dependent and mild in nature and diminished gradually on continuation of therapy over 4–6 weeks or more. A majority of the adverse events of liraglutide therapy among Indian studies are also GI related. The cumulative GI adverse events in Indian studies varies from 11.28% (Kesavadev *et al*., 2015)[14] to 63% (Kesavadev *et al*., 2012).[10] In the long-term study by Chaudhuri *et al*. (2016),[15] 8 out of 39 subjects (20.51%) complained of GI events. Majumder *et al*. (2017)[19] highlighted the benefit of starting with a very low dose (0.2 mg). Though statistically not superior, starting with 0.2 mg liraglutide and weekly up-titration appeared to be better tolerated, with lower dropout rates, owing to lesser GI intolerance.

The risk of hypoglycemia as reported in the LEAD program was low across all the treatment arms and especially increased in combination with sulphonylureas (0.47–1.93 events per patient per year in LEAD-1, LEAD-5, and LEAD-6). Interestingly, the rate of minor hypoglycemia was significantly less with liraglutide plus OADs compared with exenatide plus OADs in LEAD-6. No major hypoglycemic episodes were reported in LEAD-4, the 26-week LEAD-2 main study phase and the 52-week LEAD-3 main study phase.[4-9,20] Similarly, no hypoglycemic episodes were reported from short-term Indian studies except 3% mild hypoglycemia events reported from Kaur *et al*. (2016).[12]

In the long-term study by Chaudhuri *et al*. (2016),[15] no documented hypoglycemia for any of the subjects was observed; however, two subjects reported subjective hypoglycemia-like symptoms which was not confirmed by a glucometer reading. It will be worthwhile to note that a vast majority of the patients in this study were initiated with a strategy of gradual up-titration from a very low-dose (0.2 mg) liraglutide as followed in Majumder *et al*.[19] and thus has also showed much lesser GI adverse events than in other published Indian studies.

As seen in the LEAD program, the Indian studies also reported similar GI adverse events and low risk for both major and minor hypoglycemias. The GI side effects was maximum in the initial 3 months leading to GI-related dropouts but were insignificant after 6 months of therapy.

Conclusion

Liraglutide therapy improved glycemic control with low risk of hypoglycemia and facilitated clinically relevant weight loss in both short- and long-term real-world studies among Indian subjects with T2DM. The glycemic efficacy and weight loss seen in Indian studies are far more impressive than seen in the LEAD program. Liraglutide therapy, at a much lower dose than 3 mg daily, also significantly improved weight loss in obese non-diabetic Indian subjects. The frequency of GI adverse effects in the Indian real-world studies was nearly in

accordance with the results seen in the LEAD trials. Most of GI side effects and GI adverse event related drop outs were observed in the initial 3–6 months starting of therapy. When tolerated for initial three-six months, liraglutide therapy was associated with minimal GI side effects and no GI adverse event related dropout in the Indian real world studies. Moreover, starting with a very low-dose (0.2 mg) liraglutide and weekly up-titration appears to be better tolerated and further reduces the GI adverse event related dropouts.

Conflicts of interest
There are no conflicts of interest.

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