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ORIGINAL ARTICLE

Efficacy and safety of liraglutide in Indian adolescents with obesity

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Summary

Aim

The aim of this study was to evaluate the efficacy and safety of liraglutide in adolescents with obesity.

Materials and methods

Patients (n = 41) received injection liraglutide for at least 12 weeks and their pre-baseline and post-baseline characteristics were recorded and analysed. The key parameters analysed were weight, height, body mass index (BMI), fasting insulin and sugar, 1 h insulin and glucose, 2 h insulin and glucose, HbA1c, cholesterol, triglycerides, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, thyroid stimulating hormone and bone.

Results

There was a significant decrease ($p < 0.001$) in body weight, BMI, fasting, 1 h post-glucose tolerance and 2 h glucose tolerance. The changes from baseline to the end of study were for body weight − 6.5 ± 4.2 kg and BMI –2.35 ± 1.30 kg m^{-2}. Systolic blood pressure decreased from 119.25 ± 12.50 to 114.53 ± 9.53 mmHg and diastolic blood pressure from 70.69 ± 14.52 to 70.82 ± 8.85 mmHg. Liver enzymes had improved from 34.36 ± 12.23 (serum glutamic oxaloacetic transaminase), 38.08 ± 21.02 (serum glutamic pyruvic transaminase) to 33.52 ± 11.23 (p = 0.03) and 33.99 ± 13.16 (p = 0.01), respectively. Cholesterol and triglyceride had improved from 152.46 ± 24.74 and 124.41 ± 33.27 to 151.71 ± 23.46 (p = 0.14) and 120.76 ± 26.22 (p = 0.009), respectively.

Conclusion

In conclusion, treatment with liraglutide in adolescents with obesity offers an efficacious and safe alternative to patients who are not responding to other available modalities.

Keywords: Adolescents, liraglutide, obesity, GLP-1.

Introduction

Childhood obesity acts as a predisposing factor for future non-communicable diseases (1). In 2015, a total of 107.7 million children and 603.7 million adults were living with obesity. Since 1980, the prevalence of obesity has doubled in more than 70 countries and has continuously increased in most other countries (1). In India, analysis of data after 2010 estimates a combined prevalence of 19.3% of childhood overweight and obesity, which was a significant increase from the earlier prevalence of 16.3%, reported in 2001–2005 (2). There is an increasing prevalence of severe obesity associated with serious medical and psychosocial comorbidities. Hypertension, dyslipidaemia, arterial stiffness, endothelial dysfunction/activation, myocardial dysfunction, elevated levels of inflammation and oxidative stress, insulin resistance, impaired glucose tolerance, obstructive sleep apnoea, sease and psychosocial problems such as depression and anxiety are a few important comorbidities that are associated with obesity (3,4).

Recent data show that in developed countries, children in lower income families are more prone for development of obesity because of low nutritious diet and

limited opportunities to physical activity, while in developing countries, it is more prevalent in wealthier sections of the populations. However, childhood obesity is also on the rise among urban poor population, which can be related to westernized diets with a history of under-nutrition (5).

Interventions available for paediatric obesity are very limited. Three major intervening modes are lifestyle interventions, pharmacotherapy and bariatric surgery. Lifestyle modification interventions include three components: caloric restriction, increased physical activity and behavioural modification counselling. For the treatment of childhood obesity, the behavioural modification counselling is often delivered to the family. Although it is the first line treatment, it is not effective especially in adolescent population, while in younger population, it might offer a better response (6–10). One large study reports a success rate of only 20% with lifestyle interventions in adolescent with extreme obesity (6). These findings indicate the unmet need for pharmacological interventions required in adolescents with obesity.

The only approved pharmacotherapy for adolescents with obesity is orlistat; despite the fact that it has a significant effect on weight loss, a large number of patients remain to have non-significant effect on weight loss (11). Another medication, which has been used widely for the treatment of type 2 diabetes used for obesity with insulin resistance, albeit off label as well, is 'metformin'. Various studies report beneficial effect in terms of weight loss with metformin (12). Despite the various studies in this population showing the effect of aforementioned two medicines, there are a great number of adolescents with obesity who remain to struggle with obtaining a significant weight loss that leads to a clinician to look forward to the anti-obesity medication approved for adult population; such a medicine that has been recently tested for adolescent population as well as on a pilot basis is liraglutide. It is a GLP-1 analogue, which has a possible weight loss by multiple mechanisms, by acting on the hypothalamic satiety centre and one of it being by upregulation of adenylate cyclase 3 (13).

Our institute developed an institutional guideline to help adolescents with obesity, where we decided to give option of liraglutide to our adolescent patients with obesity, who did not respond to lifestyle interventions and orlistat and metformin, each for a minimum period of 12 weeks. After taking written informed consent from these patients, they were started on injection liraglutide. This study retrospectively evaluates the efficacy and safety of injection liraglutide in adolescents with obesity. This study predominantly aims to demonstrate the weight benefits of GLP1 receptor agonist liraglutide in adolescents with obesity.

Methods

Study design

This was a 36-week, non-randomized, open-label study involving retrospective data collection from 356 adolescents (age 12–18 years) with obesity (BMI $>$ 95th percentile or $>$27 adult equivalent as per age and sex specific Indian Academy of Pediatrics growth chart) with Tanner Staging 2–5 (Figure 1). All the patients attended the paediatric outpatient department of the Indraprastha Apollo Hospital, Delhi, between March 2015 and December 2017. The study enrolled all adolescents with obesity who were diagnosed as simple/nutritional obesity. All these patients were initially started on lifestyle interventions, which include a low-calorie diet 1,200 kilo-calories with reduced carbohydrate and reduced fat intake and 60 min daily physical activity. Following which patients were re-evaluated after 12 weeks, and those patients who have $<$5% body weight reduction were started on tab orlistat minimum dose of 120 mg twice daily to a maximum tolerable dose up to 120 mg thrice daily before meals, and patients who have signs of insulin resistance were started on tab metformin with a dose of 10 mg kg^{-1} body weight d^{-1} initially that was increased to 20 mg kg^{-1} body weight d^{-1} with maximum dose of 2 g d^{-1} after 2 weeks after evaluating the patients for possible side effects. The key inclusion criteria were informed consent obtained before the child was started on tab metformin/injection liraglutide, male or female, age 12 to less than 18 years at the time of signing informed consent and completion of treatment, body mass index (BMI) corresponding to equal to or above 27 kg m^{-2} for adults by Indian Academy of Pediatrics guideline (same as IOTF guideline for Asian population) for definition of obesity and equal or above the 95th percentile (27 adult equivalent) for age and sex (for diagnosis of obesity), history of failing to lose sufficient weight with lifestyle modification as judged by the investigator and documented in subject's medical record.

Exclusion criteria are pre-pubertal subjects (Tanner stage 1) at screening, type 1 diabetes mellitus, family or personal history of multiple endocrine neoplasia type 2, medullary thyroid carcinoma, history of pancreatitis (acute or chronic) and subjects with secondary causes of obesity (i.e. hypothalamic, drug-induced, genetic or endocrine causes).

Patients were re-evaluated after 12 weeks, and those patients who have $<$5% body weight reductions were offered to start injection liraglutide after written informed consent. All patients who consented were investigated with oral glucose tolerance test, liver function test, serum amylase, serum lipase, and fasting lipid profile, FT4 (free

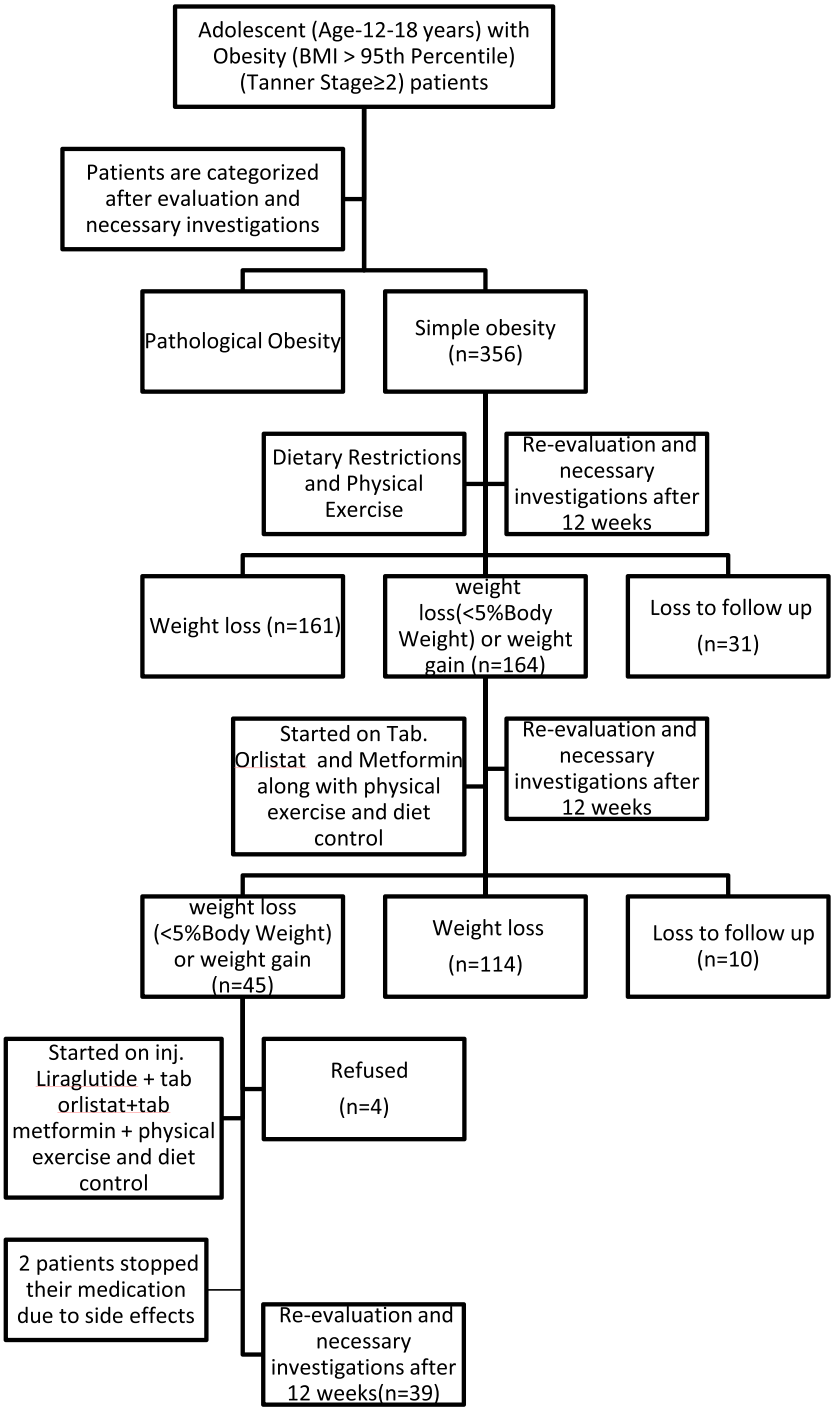

Figure 1 Study design.

thyroxine), thyroid stimulating hormone (TSH) and HbA1C (haemoglobin A1c). Bone age was evaluated using Tanner–Whitehouse method. The anthropometric data (BMI), age and blood pressure were recorded. The safety variables included episodes of hypoglycaemia (self-measured plasma glucose level < 70 mg dL^{-1}, checked as and when required), gastrointestinal disorders (nausea, abdominal pain, vomiting and diarrhoea), injection site pain or pruritis, skin and subcutaneous tissue disorders and haematoma.

Injection liraglutide was started as 0.6 mg subcutaneously 1 h before dinner that was increased 0.3 mg every

week to a maximum dose of 1.8 mg. Patients with gastrointestinal effects were advised tab pantoprazole and tab ondansetron. All the patients were evaluated and investigated again after 12 weeks of treatment.

The study was initiated after taking an approval from institutional ethics committee and was conducted in accordance with principals of the Declaration of Helsinki and ICH Good Clinical Practice.

Study endpoints

The primary endpoint of the study was change in BMI from baseline to 12 weeks. Secondary outcome includes % of subjects achieving equal to or above 5% reduction in baseline BMI, % of subjects achieving equal to or above 10% reduction in baseline BMI, change in BMI, change in body weight (kg), change in body weight (%), change in systolic and diastolic blood pressure, change in metabolic profile including glycosylated haemoglobin (HbA1c) fasting insulin and glucose, 1 h insulin and glucose, 2 h insulin and glucose, HbA1c, cholesterol, triglycerides, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), thyroid stimulating hormone (TSH) and bone age, number and frequency of treatment emergent adverse events.

Statistical analyses

Changes from baseline to week 12 for weight, height, BMI, fasting insulin and glucose, 1 h insulin and glucose, 2 h insulin and glucose, HbA1c, cholesterol, triglycerides, SGOT, SGPT, TSH and bone age were analysed using paired *t*-test to test if there was a significant difference between baseline and week 12. The *t*-test was used to test significant difference between male and female patients.

Results

Forty-five adolescents who met the selection phase characteristics were counselled for the intervention, and 41 gave their informed written consent and started on injection liraglutide. Twenty-two subjects were female and 19 were male, with mean chronological age of 15.5 ± 1.9 years (male and female chronological age 16.16 ± 1.80 and 15.13 ± 1.97, respectively) and mean weight, mean BMI of 94.11 ± 20.19, 34.17 ± 4.89, respectively. Two subjects were removed from the study, due to severe gastrointestinal side effects. Thirty-nine patients completed the study with a treatment adherence >90% that included taking the study medication and coming for study assessments.

There was a significant decrease in body weight, BMI, fasting, 1 hour post-glucose tolerance and 2 h glucose tolerance (Table 1). The changes from baseline to the end of the study were for body weight −6.5 ± 4.2 kg, BMI –2.35 ± 1.30 kg m^{-2} (Tables 2 and 3). Systolic blood pressure decreased from 119.25 ± 12.50 to 114.53 ± 9.53 and diastolic blood pressure from 70.69 ± 14.52 to 70.82 ± 8.85. Liver enzymes had improved from 34.36 ± 12.23 (SGOT), 38.08 ± 21.02 (SGPT) to 33.52 ± 11.23 ($p = 0.03$) and 33.99 ± 13.16 ($p = 0.01$) respectively (Table 4). Cholesterol and triglyceride had improved from 152.46 ± 24.74 and 124.41 ± 33.27 to 151.71 ± 23.46 ($p = 0.14$) and 120.76 ± 26.22 ($p = 0.009$) respectively (Table 4). Bone age was not increased significantly after 3 months of treatment. There was no significant increase in amylase, lipase and LDH levels. HbA1C was decreased from 5.32 ± 0.26 to 5.19 ± 0.15 ($p < 0.001$).

Adverse events (Table 5) observed were nausea (71.7%), vomiting (41%), decrease in appetite (69.2%), diarrhoea (20.5%), nonspecific abdominal pain (15.3%) and injection site pain or pruritis (5.1%).

Discussion

The present observational study aims to evaluate efficacy and safety of liraglutide, a GLP-1 analogue, among adolescents with obesity who did not respond to physical exercise and diet control (12 weeks) and orlistat and metformin (12 weeks). During the study, adolescents with obesity showed a significant decline in their weight, BMI and metabolic profile with minimal tolerable side effects.

Table 1 Baseline BMI

Pre-difference to post-difference	Mean difference	SD	95% confidence interval of the difference		*t*-value	*p*-value
			Lower	Upper		
BMI	2.35688	1.30632	1.93342	2.78034	11.267	<0.001
z-score SDS BMI	0.34077	0.16161	0.28838	0.39316	13.168	<0.001

BMI, body mass index.

Table 2 Change in BMI

	% change in BMI	BMI change (absolute)	Change in *z*-score
Mean	6.56	2.36	0.34
SD	2.97	1.31	0.16

BMI, body mass index.

Table 3 Percentage change in BMI

% change in BMI	No. of patients	%
>10%	9	23.08
5–10%	20	51.28
<5%	10	25.64
Total	39	100

BMI, body mass index.

Efficacy and safety are essential in any treatment of any paediatric population. There are only two small studies, which have evaluated the efficacy of liraglutide in adolescent non-diabetic patients with obesity, whereas there are several adult studies are available. In the present study, weight loss was 6.56 ± 2.97%, absolute weight loss was 6.5 ± 4.2 kg, and BMI was decreased by 2.35 ± 1.30 kg m^{-2}. A study in adolescent population with obesity showed body weight decrease by 2.5 kg (−3.1 to −1.9) and BMI −0.9 kg m^{-2}(−1.2 to −0.7) following a dose of 1.2 mg once daily liraglutide for 48 days(14), another study in adolescent obese shows BMI *z*-score decrease by −0.12 and body weight −2.55 kg over a period of 5 weeks with starting dose of 0.6 mg daily to weekly increment of 0.6 mg to maximum dose of 3.0 mg (15); while in our study while dose was 1.8 mg and period of study was 108 d (12 weeks) so results are comparable with our study.

Table 5 Adverse events

	Adverse event	% (No.)
1	Hypoglycaemia	None
2	Gastrointestinal disorders	92.3 (32)
a	Nausea	71.7 (28)
b	Abdominal pain	15.3 (6)
c	Vomiting	41.0 (16)
d	Diarrhoea	20.5 (8)
3	Decrease in appetite	69.2 (27)
4	Injection site pain or pruritis	5.1 (2)
5	Skin and subcutaneous tissue disorders	0
6	Headache	0

One of the biggest and longest adult clinical trial (Satiety and Clinical Adiposity-Liraglutide Evidence in individuals with and without diabetes [SCALE] programme) of liraglutide in patients without diabetes and with obesity shows weight loss of 8.4 ± 7.3 kg (−8.0 ± 6.7%, −3.0 ± 2.6 kg m^{-2}) over a period of 52 weeks with liraglutide dose of 3.0 mg (16), which is less as compared to our study and can be explained on the basis that adult and adolescent react differently to the each intervention, while our results are comparable to adolescent population studies and far better than adult studies.

Our study shows 23.08% patients had >10% weight loss and 51.28% patients had weight loss between 5% and 10%, while 25.64% had weight loss of <5% that may be due to the unrecognized genetic background of obesity that might not have been detected.

Secondary outcome of this includes oral glucose tolerance test, which shows significant reduction in blood glucose and insulin level after 3 months of injection liraglutide. Study by Danne *et al*. shows decrease in fasting plasma glucose by −3.51 mg dL^{-1} (−0.19 mmol L^{-1}), HbA1c

Table 4 Change in other parameters

			Pre-difference	Post-difference	Mean difference	*p*-value
1	Blood pressure	Systolic	119.25 ± 12.50	114.53 ± 9.53	4.23 ± 11.08	0.013
		Diastolic	70.69 ± 14.52	70.82 ± 8.85	0.10 ± 13.23	0.951
2	Insulin	Fasting	25.57 ± 20.00	21.07 ± 16.75	5.07 ± 3.22	<0.001
	(mIU mL^{-1})	1 h	102.20 ± 68.66	81.41 ± 57.58	18.25 ± 10.13	<0.001
		2 h	91.09 ± 68.68	68.68 ± 50.04	17.04 ± 10.79	<0.001
3	Sugar	Fasting	86.24 ± 6.86	80.74 ± 6.81	5.50 ± 0.69	<0.001
	(mg dL^{-1})	1 h	135.68 ± 20.18	126.62 ± 19.85	9.06 ± 1.18	<0.001
		2 h	123.39 ± 14.46	116.91 ± 14.42	6.47 ± 0.81	<0.001
4	Liver enzymes	SGOT	34.36 ± 12.23	33.52 ± 11.23	0.81 ± 2.45	0.03
		SGPT	38.08 ± 21.02	33.99 ± 13.16	3.40 ± 9.28	0.01
5	Lipid profile	Cholesterol	152.46 ± 24.74	151.71 ± 23.46	0.50 ± 2.76	0.14
		Triglyceride	124.41 ± 33.27	120.76 ± 26.22	3.34 ± 8.18	0.009
6	HbA1c		5.32 ± 0.26	5.19 ± 0.15	0.13 ± 0.16	<0.001

SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

−0.11% (−1.22 mmol mol^{-1}) and mean fasting serum insulin levels decreased by −1.43 mIU mL^{-1} (−10.22 pmol L^{-1}), which are low as in comparison with our study that can be explained by the concomitant use of orlistat and metformin in our patients. Our patients also have very high initial levels of insulin as usually seen in Indian population. None of the adolescent study reports oral glucose tolerance test comparison before and after the study.

Other parameters, which were compared – liver enzymes, fasting lipid profile, systolic and diastolic blood pressure – were decreased (cholesterol and SGOT decrease were non-significant), while in SCALE trial (16) among adult population, all were decreased, but short-term adolescent study (14) do not show significant decrease in cholesterol and triglycerides.

Safety profiles of liraglutide have been studied among adult population thoroughly, and hypoglycaemia is one of the feared adverse events reported to be associated with liraglutide in both adult and adolescent population (14,16). Our study patients did not report any spontaneous hypoglycaemia episodes during 12 weeks period of liraglutide administration; while Danne *et al*. report two out of 14 patients having confirmed hypoglycaemia episodes, and González-Ortiz *et al*. did not report any hypoglycaemic event using 1.8 mg daily dose, which suggests that 1.8 mg dose may not be associated with hypoglycaemia.

Most common adverse event noted is gastrointestinal disorders such as nausea (most common), abdominal pain, vomiting and diarrhoea similar to other studies as reported in adults and adolescents. Amylase and lipase were evaluated before and completion of 12 weeks of treatment but did not show statistically significant increase in either of them.

Limitations of this study include small size, open-label, non-randomized and short duration of treatment. Although results here are promising especially for adolescents with obesity who are not responding to other available modalities, it is difficult to determine long-term efficacy of injection liraglutide, and one should be careful and vigilant in starting adolescent obese patients to the same.

In conclusion, treatment with liraglutide in adolescents with obesity offers an efficacious and safe alternative to patients who are not responding to other available modalities rather putting these patients through surgical modalities for treating obesity.

Conflict of Interest Statement

The authors declare that there is no conflict of interest and disclosures associated with this manuscript.

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