DOI: 10.4274/jcrpe.galenos.2024.2023-10-10

Research Article

Liraglutide Treatment Improves Glycaemic Dysregulation, Body Composition, Cardiometabolic Variables and Uncontrolled Eating Behaviour in Adolescents with Severe Obesity

Apperley L et al. Liraglutide Treatment in Childhood Obesity

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What is already known on this topic?
Liraglutide has shown beneficial effects in adolescent obesity in clinical trials and has therefore been approved for clinical use. Continuous glucose monitoring (CGM) is routinely used in type 1 diabetes mellitus, but not for type 2 diabetes mellitus (T2DM) or obesity.

What this study adds?
We show the significant improvements following liraglutide treatment in a routine clinical setting with improvements in weight, BMI, BMI SDS, body fat percentage, fat mass, percentage time glucose levels spent within normal range, HbA1c, cholesterol, triglycerides, and uncontrolled eating behaviour in adolescents.

Abstract
Objective*:* Childhood obesity is associated with long-term health complications. Liraglutide is approved for use in adolescents for weight loss and has shown beneficial outcomes in clinical trials. Continuous glucose monitoring (CGM) is routinely used in type 1 diabetes mellitus. We aimed to look at the effect of liraglutide treatment on cardiometabolic variables, glycaemic control (as assessed by CGM), body composition, quality-of-life and satiety levels in adolescents with severe obesity.
Methods*:* 24 patients aged 12 to 17.9 years (10M:14F) were commenced on liraglutide in addition to lifestyle support. PedsQL 4.0 generic scale and Three-factor Eating Questionnaire R18 were completed at baseline and 3-months.
Results*:* Significant improvements were shown in weight, body mass index, body mass index standard deviation scores, percentage body fat and fat mass following liraglutide treatment. A significant reduction in HbA1c, triglyceride and cholesterol levels, as well as a reduction in uncontrolled eating behaviour were observed. When compared to the healthy adolescents, the time spent within normal glucose range (3.9-7.8mmol/L; 70.2-140.4 mg/dL) remained low (91.76% vs 97.00%) at baseline but improved after liraglutide treatment. Our results showed lower health-related quality-of-life scores and higher uncontrolled eating and emotional eating behaviours, compared to the healthy population.
Conclusion*:* We report, for the first time, the role of CGM in identifying glycaemic dysregulation in children and young people with obesity before and after liraglutide treatment. The results have shown significant potential for liraglutide treatment in improving the outcomes. Earlier identification of glycaemic dysregulation and targeted therapy could potentially reduce the long-term risk of developing T2DM.
Keywords: Liraglutide, glycaemic dysregulation, adolescents, obesity

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30.10.2023
05.09.2024

Published: 23.09.2024

Introduction

Childhood obesity remains a worldwide concern due to its rising prevalence and associated complications. Type 2 diabetes mellitus (T2DM) is a chronic condition that has a number of related long-term issues such as micro- and macrovascular diseases (1). It has been shown that children and young people (CYP) with obesity are at a four-fold increased risk of developing T2DM (2, 3).
Treatment options for obesity within the paediatric population remains limited, with lifestyle intervention being first line. Liraglutide, a glucagon-like peptide 1 analogue, has received EMA and FDA approval for adolescents aged 12-17 years with a body weight of at least 60kg and an initial body mass index (BMI) corresponding to 30kg/m^2 or greater for adults (4, 5). It has been shown to have a significant effect on BMI standard deviations scores (SDS) and glycated haemoglobin (HbA1c) in adolescents (6, 7, 8, 9). The efficacy and tolerability in adolescents have been reported as similar to those seen in adults, with no unexpected issues found (8, 9, 10). Liraglutide has both central and peripheral mechanisms of action, which result in slower gastric emptying, thus increased satiety, and increased insulin production (11).
In view of liraglutide's potential to improve glycaemic control and the concerns of the increasing cases of T2DM secondary to childhood obesity, there is need for further research within this area. The introduction of continuous glucose monitoring (CGM) for patients with type 1 diabetes mellitus has been beneficial and reports in adults show the potential for its use in T2DM to improve glycaemic control and reduce complications (12). The use of CGM to investigate glycaemic dysregulation in childhood obesity is limited, and to our best knowledge it has not been used in normoglycaemic CYP with obesity who have received liraglutide treatment.
The aim of our study is to investigate the effect of 3-months liraglutide treatment on glycaemic control, anthropometry, metabolic outcomes, quality of life and satiety levels, in children and young people with obesity.

Methods

This was a retrospective study over a period of 18 months where 24 patients have been commenced on liraglutide (Saxenda) and followed regularly to assess the progress (Figure 1). All patients were under the care of the tier 3 multi-disciplinary weight management service at a tertiary children's hospital and received lifestyle intervention in the outpatient setting. Two patients had T2DM, and one patient had impaired glucose tolerance.

The anthropometric measurements and fasting cardiometabolic variables were performed on a regular basis. The CYP had a CGM device inserted and completed three questionnaires at baseline and at 3-months post liraglutide treatment to investigate the effects of the treatment in a routine clinical setting.

Measurements

The CYP had their weight, BMI and BMI SDS measurements undertaken by the same staff in the medical day case unit. The body composition was obtained using a TANITA: RD-545HR device, which reported body fat percentage (%), fat mass (kg) and free fat mass (kg).

Biochemistry

Fasted blood samples were taken at each time point for HbA1c, insulin, c-peptide, liver enzymes (aspartate aminotransferase and alanine transaminase) and lipid profile. If the patient was not fasted then the insulin, c-peptide and triglyceride levels were omitted from analysis.

Continuous Glucose Monitoring (CGM)

Continuous glucose monitoring was used at these time periods to investigate alterations in glycaemic dysfunction following the use of liraglutide. Dexcom G6 CGM devices were used for the majority of the CYP. Two CGM data sets were collected using FreeStyle Libre Pro devices. All devices were placed onto the upper arm of the patients and removed on day 10 for the Dexcom wearers and day 14 for Libre wearers. When analysing the data, the readings for the first 12 hours were omitted to ensure accuracy.

Questionnaires

The patients and guardians were asked to complete the following questionnaires at baseline and 3-months.

1. PedsQL Paediatric Quality of Life Inventory Version 4.0 – English (UK): Child or teenager report (13)
2. PedsQL Paediatric Quality of Life Inventory Version 4.0 – English (UK): Parent/Guardian report (13)

Both the above questionnaires assess the quality of life for the participants. They have questions that investigate physical functioning, emotional functioning, social functioning, and school functioning. Transformed scores (0-100) are produced from the raw scores and the mean value is calculated. The higher the score indicates the better quality of life. From these, the psychosocial health summary score, physical health summary score and total score are also calculated.

3. Three Factor Eating Questionnaire R18 (TFEQ-R18) (14, 15)

This questionnaire is completed by the participants and investigates their levels of uncontrolled eating, cognitive restraint, and emotional eating. Each statement has a score dedicated to one of the sections and the raw score is converted to a transformed score (0-100).

Liraglutide

Liraglutide was commenced following the baseline CGM at a dose of 0.6mg once daily as a subcutaneous injection and increased in stages up to the maximum dose of 3mg, or highest tolerated dose, with the support of the specialist nurse.

Statistics

The measurements, blood investigations and questionnaire results were analysed using a paired sample t-test to compare the means of each time point. The average glucose and the standard deviation from the CGM data was also analysed using a paired sample t-test. The percentage time that glucose levels were in and out of range were analysed using the Wilcoxon Signed Ranks Test to compare the medians at baseline and 3-months post-liraglutide treatment. All statistical analysis was completed using IBM SPSS version 27.

Results

The average age of the patients was 14.7 years (range: 12-17.9 years) and 14/24 (58.3%) were female. The average measurements at baseline and 3-months are shown in Table 1. A significant mean weight reduction was shown (-2.95kg, p=0.001), along with a significant decrease in the mean BMI and BMI SDS (-1.38kg/m^2; p<0.001 and -0.09; p=0.003, respectively). Body composition was performed, which evaluates body fat percentage, fat mass and free fat mass. A significant reduction was seen over the course of the 3-months of liraglutide treatment in body fat percentage (-2.09%; p=0.043) and fat mass (-4.00kg; p=0.011).

The biochemistry results showed a reduction in HbA1c, insulin, liver function and lipid profile levels [Table 2]. Significant reductions in HbA1c (-1.35mmol/mol; -2.3% (DCCT), p=0.025), triglycerides (-0.122mmol/L; p=0.010) and cholesterol (-0.28mmol/L; p=0.029) were noted over the 3-month treatment course. The change in HDL cholesterol levels were not significant, but the mean result went from being in the abnormal range to normal range over the course of 3 months.

The CGM devices were worn for an average of 9.12 days (range: 2.2-13.9). The mean glucose level reduced slightly over the treatment course with an average glucose of 6.56mmol/L (118.1mg/dL) at baseline and 6.50mmol/L (117.0mg/dL) at 3-months (p=0.828). The standard deviation calculated by the CGM device improved from 1.11mmol/L to 0.97mmo/L (20.0-17.5mg/dL), which was not quite significant (p=0.066) [Table 3a]. The median percentage time that the patient's glucose levels were within normal range (3.9-7.8mmol/L; 70.2-140.4mg/dL) significantly improved with liraglutide treatment as it increased from 91.76% to 94.18% (p=0.048). It was also noted that the percentage time that glucose levels were >7.8mmol/L (140.4mg/dL) or >10mmol/L (180 mg/dL) also reduced during the intervention period [Table 3b]. These results show that the use of liraglutide does improve glucose variation in CYP with obesity. When compared to 12-18 year olds who are healthy, with a BMI below the obesity threshold and do not have diabetes, the time spent with glucose levels within the normal range remained lower in our cohort (97.00% vs 91.76% and 94.18%) (16) [Table 3b].

Quality of life was measured through both child and parent-reported questionnaires and the mean transformed scores were calculated. The child-reported scores showed an improvement in all sections, except for social functioning, which remained similar. None of the improvements were found to be statistically significant [Table 4]. The parent-reported scores also showed an increase in quality of life for all areas, except for school functioning. Even though an overall positive change was noted, the results remain much lower than those reported by Upton et al, which represents healthy children and parents and also those with a chronic condition (17) [Table 4]. This highlights the association between childhood obesity and lower quality of life levels.

Liraglutide is known to improve satiety (11) and this has been shown by the results of the TFEQ-R18 scores. A significant reduction was seen in uncontrolled eating with a mean baseline score of 51.94 and 3-month score of 41.01 (-10.93; p=0.006). Cognitive restraint increased and emotional eating reduced over the 3-months, but the differences were not statistically significant [Table 4].

Discussion

The results show the significant improvements following liraglutide treatment in a routine clinical setting with improvements in weight, BMI, BMI SDS, body fat percentage, fat mass, percentage time glucose levels spent within normal range, HbA1c, cholesterol, triglycerides and uncontrolled eating behaviour in adolescents.

The change in weight, BMI and BMI SDS in our results support those found in clinical trials (7, 18, 19, 20). Zhao et al recently published a systematic review and meta-analysis comparing medications for the treatment of obesity. Compared to metformin, orlistat, exenatide and topiramate, liraglutide had shown to be the most beneficial treatment for weight loss in children and young people (21). Our results show a significant reduction in body fat percentage and fat mass. The effect of liraglutide on body composition has been shown in adults by the use

of dual energy X-ray absorptiometry (22, 23, 24). Feng et al showed a significant reduction in total fat mass, trunk, limb, android and gynoid fat following a 24-week course of liraglutide treatment (1.8mg) in adult patients with T2DM and non-alcoholic fatty liver disease (22). Significant reductions in total body fat, visceral adipose tissue and liver fat were seen following a median course of 36 weeks of liraglutide (3mg) versus placebo by using MRI scanners (25). These changes are thought to reduce the risk of cardiovascular disease complications (25). There are very limited studies available looking at the effect liraglutide has on body composition in the paediatric population. Our results are promising after 3-months of treatment. Liraglutide likely has this positive effect on body composition secondary to its known mechanisms (lower plasma glucagon levels, delayed gastric emptying and increased satiety). It has been suggested that there may also be a weight independent effect of liraglutide on the distribution of body fat (25). Further research is needed in this area, especially in CYP.
Kelly et al had not shown significant changes in glycaemic and cardiometabolic variables (7), but interestingly our results do not support this. We have shown improvements in all the biochemical variables, except for fasting c-peptide levels. HbA1c, triglyceride and cholesterol levels reduced significantly, and even though the difference was not significant for HDL-C it had improved from the abnormal to normal range over the treatment course. Similar results have also been shown previously (19, 20). These improvements also support the potential cardiovascular benefits that liraglutide might have in the long run.
Due to its positive effect on glycaemic control, liraglutide has been approved for the treatment of T2DM in children aged 10 years and over. Fasting glucose and HbA1c levels have been analysed during liraglutide treatment and it has shown good effect compared to placebo (6).
The rising rates of childhood obesity are associated with increased prevalence of T2DM in CYP. As previously mentioned, T2DM has multiple complications which may have a significant impact on the individual. Identifying glycaemic dysregulation in CYP with obesity, who are at an increased risk, would result in commencing interventions and potentially reducing the chance of the individual developing T2DM. The use of CGM has been shown to be a feasible and acceptable tool to investigate glycaemic control in both paediatric and adult populations (26, 27). To our best knowledge, CYP with obesity, but not T2DM, on liraglutide treatment have not had their glucose levels analysed using CGM devices. Our patients tolerated the monitors well and the results show a significant improvement in the time that their glucose spent within the normal range following treatment. Shah et al analysed glycaemic variation in healthy children and adults and this data was used for comparison (16). The results from the 12–18-year-old participants was used as this was the same age range as our patients. At best, the median percentage time in range was 94.18%, which was still lower than the results seen in the healthy population (97.00%). Interestingly, Shah et al did not report any blood glucose levels above 10mmol/L, whereas for our patients, they had 0.08% and 0.02% of time spent above this level at baseline and 3-months, respectively (16). This shows that CYP with obesity have evidence of glycaemic dysregulation, which improves with liraglutide treatment. This highlights the potential to commence at risk individuals on treatment at the earliest point, thereby preventing them from progressing to pre-diabetes or T2DM.
Lower health-related quality of life (HR-QoL) has been shown to be associated with childhood obesity. Younger children have appeared to have scored lower in the physical functioning compared to psychosocial functioning (28). Whereas other studies have shown that the individuals' psychosocial QoL is impacted more as they get older into adolescence years and with the most severe grade of obesity (29, 30). The total score for HR-QoL improved in our cohort of patients following liraglutide treatment. For both child and parent-reported questionnaires the psychosocial score was lower than the physical health score. Adult studies have shown this association (31, 32), whereas Kelly et al did not find any difference in overall weight-related quality of life in adolescents (7). Data from Upton et al's paper was used for comparison, and the scores from the healthy population were much higher in all sections than those seen in our patients (17). This highlights the importance of psychology support within the multidisciplinary team in the management of childhood obesity.
The GLP-1 hormone acts by delaying gastric emptying and appetite suppression (7, 33). We analysed the effect of this in the clinical setting by asking our patients to complete the TFEQ-R18 questionnaire. A significant reduction was seen in uncontrolled eating behaviours and both cognitive restraint and emotional eating showed improvement during the treatment course. De Lauzon et al's work was used as the comparison healthy population. As expected, their scores for emotional and uncontrolled eating were lower than our results, but interestingly our patients had higher scores of cognitive restraint (34). Emotional eating was the highest score, which links with the poor psychosocial scores previously mentioned. These results can be used by the psychology team to help improve eating behaviours. This questionnaire can also be used when assessing a patient with suspected hyperphagia.
The limitations of this study include a small sample size, in comparison to clinical trials previously published. It is important to note that these patients are under the care of a tier 3 multidisciplinary weight management service, which has a specific inclusion criterion meaning that all patients have significantly high BMIs and associated complications. Therefore, these results show the effect of liraglutide on adolescents with severe obesity in the routine clinical outpatient setting. Due to the retrospective nature of data collection and patient engagement, some measurements and results were unavailable and the sample size (n) for each section has been highlighted throughout.

Conclusion

The results show the positive effect of liraglutide on CYP with obesity following a 3-month treatment course in a routine clinical setting. Significant improvements have been shown in anthropometric measurements, cardiometabolic variables and uncontrolled eating behaviour. We have also shown the potential use of CGM in identifying glycaemic dysregulation in CYP at risk due to obesity and the significant improvement that liraglutide has on the time that the glucose levels were spent within the normal range. Further research is needed, but there is promise for the use of CGM in identifying glycaemic dysregulation earlier, so that interventions can be targeted with the view of preventing the complications or progression to T2DM.

Author Contributions:
JP – collected the data and reviewed the draft
LA – analysed the data and wrote the draft
SS – supervised the project and finalised the draft

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Table 1: Anthropometric Measurements

Mean measurement	Baseline	3-months of liraglutide treatment	Difference	P value
Weight kg (SD) [n=24]	126.37 (+19.03)	123.42 (+19.68)	-2.95	**0.001***
BMI kg/m^2 (SD) [n=23]	45.48 (+7.36)	44.10 (+7.68)	-1.38	**<0.001***
BMI SDS (SD) [n=23]	3.81 (+0.47)	3.72 (+0.54)	-0.09	**0.003***
Fat Percentage % (SD) [n=19]	52.37 (+10.06)	50.27 (+9.55)	-2.09	**0.043***
Fat Mass kg (SD) [n=16]	65.05 (+19.55)	61.06 (+18.80)	-4.00	**0.011***
Free Fat Mass kg (SD) [n=16]	60.71 (+14.19)	62.28 (+13.37)	1.56	0.260

*statistically significant

Table 2: Biochemistry Results

Mean value	Baseline	3-months of liraglutide treatment	Difference	P value
HbA1c mmol/mol (SD) % DCCT [n=23]	35.39 (+3.58) 5.4 (+2.5)	34.04 (+3.11) 5.3 (+2.4)	-1.35 2.3	**0.025***
Fasting insulin pmol/L (SD) [n=19]	251.11 (+118.19)	241.37 (+129.71)	-9.74	0.723
Fasting c-peptide pmol/L (SD) [n=19]	1480.37(+462.46)	1486.16 (+555.17)	+5.79	0.950
AST iu/L (SD) [n=22]	21.77 (+9.16)	21.55 (+11.40)	-0.23	0.877
ALT iu/L (SD) [n=22]	33.14 (+28.38)	30.95 (+21.81)	-2.18	0.367
Triglycerides mmol/L (SD) [n=18]	1.02 (+0.40)	0.89 (+0.38)	-0.12	**0.010***
Cholesterol mmol/L (SD) [n=21]	4.30 (+1.07)	4.01 (+0.91)	-0.28	**0.029***
LDL Cholesterol mmol/L (SD) [n=21]	2.67 (+1.01)	2.57 (+0.81)	-0.10	0.406
HDL Cholesterol mmol/L (SD) [n=21]	1.13 (+0.20)	1.52 (+2.14)	+0.39	0.416

*statistically significant

Table 3a: Average glucose and standard deviation during continuous glucose monitoring period (n=18)

Mean Value	Baseline	3-months of liraglutide treatment	Difference	P value	Comparison data (USA) (16)
Glucose mmol/L (SD) mg/dL (SD)	6.56 (+1.18) 118.1 (+ 21.2)	6.50 (+1.16) 117.0 (+ 20.9)	-0.06 -1.1	0.828	5.4 97.2
Standard deviation of glucose provided by CGM mmol/L (SD) mg/dL (SD)	1.11 (+0.46) 20.0 (+ 8.3)	0.97 (+0.30) 17.5 (+ 5.4)	-0.14 -2.5	0.066	0.8 14.4

Table 3b: Percentage glucose time in and out of range during continuous glucose monitoring period (n=18)

Median Value	Baseline	3-months of liraglutide treatment	*Z* statistic	P value	Comparison data (USA) (16)
Percentage time <3.9mmol/L	0.26 (0.03-1.64)	0.26 (0.00-0.85)	-0.052	0.959	1.7 (0.6-2.0)

[70.2 mg/dL] (IQR)					
Percentage time 3.9-7.8mmol/L [70.2-140.4 mg/dL] (IQR)	91.76 (74.97-96.74)	94.18 (84.38-97.33)	-1.98	**0.048***	97.0 (95.0-68.0)
Percentage time >7.8mmol/L [140.4 mg/dL] (IQR)	6.82 (1.07-24.72)	4.89 (0.65-15.62)	-1.72	0.085	1.2 (0.3-2.0)
Percentage time >10mmol/L [180 mg/dL] (IQR)	0.08 (0.00-2.06)	0.02 (0.00-0.70)	-1.50	0.133	0.0 (0.0-0.0)

*statistically significant

Table 4: Quality-of-life and Satiety Questionnaire Results

Questionnaire	**Mean score at baseline (SD) [0-100]**	**Mean score at 3-months (0-100)**	**Difference**	**P value**	**Comparison data (UK) (17)**
Child/Young Person reported PedsQL [n=14]					
Physical Functioning	54.99 (+24.61)	62.59 (+28.36)	+7.60	0.11	86.08 (+14.06)
Emotional Functioning	50.12 (+29.07)	58.21 (+27.92)	+8.10	0.19	76.99 (+18.43)
Social Functioning	60.00 (+31.74)	59.29 (+32.57)	-0.71	0.84	86.85 (+16.86)
School Functioning	41.79 (+27.64)	51.07 (+26.25)	+9.29	0.16	77.29 (+16.92)
Psychosocial Health Summary Score	50.63 (+25.93)	56.19 (+27.16)	+5.56	0.23	80.50 (+14.06)
Physical Health Summary Score	54.99 (+24.61)	62.59 (+28.36)	+7.60	0.11	86.08 (+14.06)
Total Score	51.73 (+24.71)	57.79 (+26.54)	+6.07	0.14	82.25 (+13.09)
Parent reported PedsQL [n=15]					
Physical Functioning	49.58 (+28.52)	50.00 (+25.58)	+0.42	0.90	84.99 (+16.08)
Emotional Functioning	38.33 (+29.68)	41.00 (+20.37)	+2.67	0.50	74.67 (+17.67)
Social Functioning	44.67 (+30.26)	50.67 (+35.20)	+6.00	0.08	84.62 (+17.24)
School Functioning	43.33 (+23.80)	40.00 (+22.44)	-3.33	0.50	77.72 (+18.50)
Psychosocial Health Summary Score	42.11 (+24.30)	43.89 (+21.01)	+1.78	0.52	79.00 (+14.70)
Physical Health Summary Score	49.58 (+28.52)	50.00 (+25.58)	+0.42	0.90	84.99 (+16.08)
Total Score	43.98 (+24.00)	45.42 (+21.14)	+1.44	0.54	81.12 (+13.85)
TFEQ-R18 (Child/Young Person reported) [n=15]					**Comparison Data (France) (34)**
Uncontrolled Eating	51.94 (+25.77)	41.01 (+27.53)	-10.93	**0.006***	37
Cognitive Restraint	39.63 (+17.31)	41.11 (+17.03)	+1.48	0.746	26
Emotional Eating	57.04 (+24.81)	49.63 (+28.46)	-7.41	0.308	36

*statistically significant

Figure 1: Methods Design