Liraglutide for Weight Management, Critical Analysis of Efficacy and Side effects in Non diabetic, individuals with obesity: A Comprehensive Systematic Review

Sidra Kanwal (1)  
Elham Abdullah AlEmadi (2)

(1) MBBS,FCPS, MRCGP [INT] Specialist Family Medicine, Primary Health Care Corporation, Qatar  
(2) MBBS, Arab board specialist, Primary Health Care Corporation, Qatar

Corresponding author:  
Dr. Sidra Kanwal  
Primary Health Care Corporation, Qatar  
Phone: +97450494237  
Email: skanwal1986@yahoo.com

Received: February 2021; Accepted: March 2021; Published: April 1, 2021.  

Abstract

Objective: Liraglutide is a FDA approved pharmacological option of weight loss with admissible safety profile and generally considered as a safe therapeutic. However, almost all liraglutide based studies always reported a certain number of withdrawals and serious adverse events with its weight management effect. This study was designed to evaluate the efficacy, safety, and use of all doses of liraglutide for weight management in non-diabetic persons with obesity.

Methods: The literature search was performed using Cochrane advanced search using “liraglutide”, non-diabetic, weight loss, obese, and glucagon-like peptide-1 receptor agonist in different combinations. All randomized control trials, relevant to the inclusion criteria were selected for review writing.

Results: Nine randomized controlled trials of all doses of liraglutide for weight management in non-diabetic, obese individuals were identified. Most of the trials were based on liraglutide 3.0 mg, other doses were 1.2, 1.8, and 2.4 mg. All trials concluded that the greater proportion of participants achieved about 5-10% weight loss. Trials carried out with all doses of liraglutide, concluded dose 3.0 had better weight loss outcomes. Reduction of cardiovascular risks was the most reported benefit of liraglutide administration.

The common adverse events were gastrointestinal and usually occurred in the early phase of treatment during dose escalation. The only associated concern was serious adverse events such as Pancreatitis, Cancer, Psychiatric Effects linked with all doses of liraglutide, particularly dose 3.0 and associated withdrawals.

Conclusion: All doses of liraglutide are effective in weight loss in non-diabetic, obese individuals; particularly dose 3.0 is the most effective one. Generally, liraglutide is safe for most study participants with minor gastrointestinal adverse events. The only concern is its associated serious adverse events; although, experienced by very few.

Key words: Liraglutide, glucagon-like peptide, weight management, non-diabetic, obese
Introduction

Liraglutide is a unique glucagon-like peptide-1 (GLP-1) with 97% amino acid homology to human endogenous GLP1. GLP1 is a hormone produced by the gastrointestinal L-cells as a nutrient response. It initiates many functions like low blood glucose levels, slow down of gut emptying, suppression of appetite, and increased cardiac rate. Suppression of appetite and delayed gut emptying are considered a weight reduction effect, and make this peptide a choice of weight reduction therapeutic [1, 2]. However, the pharmacokinetic profile of GLP1 is specifically limited to its natural form; the half-life of native GLP1 is less than 2 minutes in blood circulation and is rapidly degraded by other enzymes. Therefore, a modified form was created to increase its shelf life and pharmacokinetic effects. Liraglutide had a modified chemical structure; Lysine is in 34th position by replacing arginine and at 26th position C-16 palmitic acid side chain attached to lysine [1, 3]. This hormone modification induces its slow absorption from the subcutaneous tissues, enhances glucose homeostasis, and reduces body weight by reducing appetite and slowing down stomach emptying process. It is non-degradable by endogenous dipeptidyl peptidase 4 (DPP4) and correctable albumin binding. An additional benefit of extended half-life for up to 13 hours is reducing its intake requirement and required daily consumption of 1 dose only, with absolute bioavailability of 55% [1-3].

It has a dose-dependent dual beneficial effect. Liraglutide is well identified as an important medication in the management of type 2 diabetes mellitus (T2DM) for years as a therapeutic option approved by FDA 2010, and also very well sounded, recommended, and prescribed for obesity, and cardiac efficiency for both diabetic and non-diabetic individuals [2,4].

It is a well-known anti diabetic and anti obese drug. The anti diabetic required dose is 1.8mg however; a higher dose is required for weight reduction. Liraglutide 3.0mg (subcutaneous injection) mg is a well-known dose for chronic weight reduction by FDA approval [2]. Liraglutide 3.0mg for >5% - 15% of weight reduction has been approved in recent years for weight reduction in many countries. High dose human exposure has not yet reported adverse events and tissue deterioration in comparison with low doses. This 3.0 dose is recommended for BMI ≥27 kg/m² and has positive effect on obesity related comorbidities like cardiac health [1, 2] or has obesity-related comorbidities. However, it has a possibly high prevalence of gastrointestinal reactions [2]. The licensed dose for glycemic control is up to 1.8 mg daily whereas, the Liraglutide 3.0 mg has been approved as an anti-obesity therapeutic for the non-diabetic population and is widely used in the U.S and the European Union [2].

Obesity is not only a serious health problem but is associated with serious co-morbidities such as diabetes, risk of heart disease, hypertension, hyperlipidemia, stroke, cancer, and even death [4]. Obesity and metabolic disorder have the potential to increase the overall mortality rate by 30% of every increase of 5 kg/m2 of body mass index (BMI). Patients of Obese Class I (BMI 30–35 kg/m2) have reduced survival rate by an average of 2–4 years whereas Obese Class II and III patients may reduce the survival up to 8–10 years. Additionally, Obesity and associated metabolic disorders are a massive economic burden on the healthcare sector. The period between 1980 - 2014 was the major lifestyle modification period with a reported prevalence of more than double cases of obesity [6, 7]. A recent study of 2019 reported the obesity rising trend is three-fold or even more in European countries. They reported that around 50% of the adult population of Europe was obese or overweight. Obesity is now a global epidemic, affecting societies both developing and developed. In association with comorbid conditions, obesity can lead to reducing life quality [8]. Weight reduction is never an easy task for the majority of people. Countless studies, randomized trials of obesity therapeutics, lifestyle modification strategies, and surgical procedures are applied for weight reduction. However, the majority of patients can reduce weight by adapting different strategies but cannot sustain them [8, 9].

The process of lifestyle modification mainly includes restricted calorie intake and physical activity; the process is easy to initiate but hard to maintain. Also, lifestyle modification is not recommended in all obese cases, due to its ineffectivity in the long run because in obese cases the body is adapted to lower calorie burn due to lower calorific intake. In these cases of lifestyle modification, high motivation is required to sustain desirable weight change. Studies reported gradual weight re-gain even in highly motivated cases. In other options, bariatric surgery is also adopted but it’s an invasive procedure with associated surgical danger. Pharmacological agents were designed to overcome all these concerns of obese individuals. In these cases, product safety is always crucial to give a safe therapeutic option for obese patients [9]. There are very few effective and safe therapeutics available for obesity, especially for long term use with overall healthy effect on other systemic processes including reducing cardiovascular risk [9].

Liraglutide is generally considered a safe anti obese therapeutics and is one of the highly prescribed therapeutics, although, very few clinical studies are available to demonstrate its functionality in weight management of non-diabetic individuals with reported side effects [9]. In the present systemic review, we aimed to evaluate the efficacy of liraglutide in weight management among non-diabetic obese individuals and its reported side effects.
Methodology

Search Scheme, Inclusion and Exclusion Criteria
All randomized controlled trials (RCTs) that evaluated the effect of liraglutide in weight management for non-diabetic obese individuals of all treatment doses were systematically searched by advanced search methodology of “Cochrane Controlled Trials Register database” and “clinical trial.org” with no initial year restriction until October 2020.

Age restriction was imposed and data of adult age group without gender restrictions were included. All possible key words were used for data extraction to ensure all possible data collection. The applied key words were “Liraglutide, obese, non diabetics” OR “Liraglutide, obese, non diabetics, side effects” OR “Liraglutide, obese, non diabetics, adverse” and “Liraglutide, obese, non diabetics, adverse events”. No language criteria were imposed but all the included studies were published in English. No database restriction was imposed on Cochrane site extracted data, such as PubMed, Embase, and Medline. The excluded RCTs were i) duplicate studies ii) studies not fulfilling the inclusion criteria, e.g; based on liraglutide administration in diabetic individuals.

Screening and Selection of Studies
Study titles, and abstracts of retrieved data were evaluated and full text studies were accessed for further evaluation.

Data extraction and management:
One author was responsible for data extraction and evaluation with appropriate broad-spectrum search words to cover the inclusion criteria. An advanced search of the Cochrane library and clinicaltrial.org was used. Data without year restriction till October 2020 were extracted. Data extraction from all provided data sources was included without any language barriers or other limitations. Data extraction was done twice. All included studies were downloaded as complete articles by manual search to analyze complete study.

Study Outcome
To analyze weight loss by all doses of liraglutide in obese, non-diabetic individuals, and its associated adverse events

Quality assessment of extracted data
Cochrane guideline, Risk of bias was followed for data extraction and data was extracted twice with the same search words in a different time frame to get the same results to avoid any risk of bias [10].
Summary of Study Selection Process

PRISMA flow diagram, Preferred Reporting Items for Systematic Review and Meta-Analysis
RCT: Randomized Control Trial
Data base: Cochrane Central Register of Controlled Trials (CENTRAL)
<table>
<thead>
<tr>
<th>Author, year, &amp; Reference No</th>
<th>Country</th>
<th>Study participants allocated (n)*</th>
<th>Study participants completed</th>
<th>liraglutide group (n)</th>
<th>placebo group</th>
<th>liraglutide dose</th>
<th>Age (year)</th>
<th>Gender (%)</th>
<th>BMI</th>
<th>Duration</th>
<th>Study Design</th>
<th>Statistical analysis</th>
<th>% withdrawal due to Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrup A, et al. 2009 [11]</td>
<td>19 clinical research centers in eight countries across Europe</td>
<td>472/564</td>
<td></td>
<td>79/98</td>
<td></td>
<td>1.2 mg</td>
<td>18-65</td>
<td>Both</td>
<td>30-40 kg/m²</td>
<td>20 weeks</td>
<td>double-blind, placebo-controlled</td>
<td>Analysis of covariance</td>
<td>Liraglutide 1.2 mg: 4 (4.2%)</td>
</tr>
<tr>
<td>Astrup A, et al. 2012 [12]</td>
<td>19 clinical research centers in eight countries across Europe</td>
<td>365 completed 1 year, 268 completed 2 years</td>
<td></td>
<td>57/60</td>
<td></td>
<td>15.0 mg</td>
<td>18-65</td>
<td>Both</td>
<td>30-40 kg/m²</td>
<td>2 years</td>
<td>double-blind, placebo-controlled</td>
<td>Analysis of covariance</td>
<td>Liraglutide 1.2 mg: 17 (18%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17.4 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Liraglutide 2.4 mg: 27 (29%)</td>
</tr>
<tr>
<td>Janssen Research &amp; Development, LLC [13]</td>
<td>Belgium, Canada, Poland, Sweden, United Kingdom, United States</td>
<td>444</td>
<td></td>
<td>115/119</td>
<td></td>
<td>3.0 mg</td>
<td>18 - 70</td>
<td>Both</td>
<td>greater than or equal to (&gt;=) 35</td>
<td>26 weeks</td>
<td>Randomized Double blind control trial</td>
<td>Difference of least square (LS) Means</td>
<td>None</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Participants</td>
<td>Mean Age (Years)</td>
<td>Gender</td>
<td>Randomization</td>
<td>Follow-up (Weeks)</td>
<td>Primary Endpoint</td>
<td>Type of Trial</td>
<td>Analysis of Covariance</td>
<td>Statistical Test</td>
<td>Analysis of Covariance</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------------</td>
<td>--------------</td>
<td>------------------</td>
<td>--------</td>
<td>-----------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>----------------------</td>
<td>---------------------</td>
<td>----------------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>Adam B. et al., 2016 [14]</td>
<td>Canada</td>
<td>359</td>
<td>48 ± 6</td>
<td>Male: 71.9%</td>
<td>40 sites in the USA and Canada</td>
<td>32 weeks</td>
<td>39.1 kg/m²</td>
<td>Randomized double-blind trial</td>
<td>Analysis of covariance</td>
<td>246 (8.9%)</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Xavier P. et al., 2015 [15]</td>
<td>Europe, North America, South America, Asia, and Australia</td>
<td>3731 patients</td>
<td>30+ mg</td>
<td>Female: 78.7%</td>
<td>Randomized double-blind trial</td>
<td>68 weeks</td>
<td>38-388.4 kg/m²</td>
<td>Double-blind, placebo controlled trial</td>
<td>Analysis of covariance</td>
<td>35.9 (12.7%)</td>
<td>42 weeks</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Robert S. et al., 2015 [16]</td>
<td>Malaysia</td>
<td>42</td>
<td>30 mg</td>
<td>Male: 21.3%</td>
<td>30 mg mg</td>
<td>12 weeks</td>
<td>30.9 ± 9</td>
<td>Randomized, double-blind trial</td>
<td>Analysis of covariance</td>
<td>359 (18.5%)</td>
<td>56 weeks</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Wadden TA. et al., 2013 [17]</td>
<td>US and Canada</td>
<td>305422</td>
<td>30 mg</td>
<td>Male: 16%</td>
<td>1.8 mg</td>
<td>30 weeks</td>
<td>Men's BMI 20 k</td>
<td>Single center randomized, placebo controlled trial</td>
<td>Analysis of covariance</td>
<td>1.8 (2.2%)</td>
<td>30--40 weeks</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Jovan C. et al., 2014 [18]</td>
<td>The Netherlands</td>
<td>44449 patients</td>
<td>30 mg</td>
<td>Both: 30%</td>
<td>18-75 mg</td>
<td>30 weeks</td>
<td>Both's BMI 20 k</td>
<td>Crossover study, incomplete</td>
<td>Analysis of covariance</td>
<td>0.6 (1.5%)</td>
<td>Both</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Chien-An Chiu et al., 2020 [19]</td>
<td>Taiwan</td>
<td>48</td>
<td>0.3 mg</td>
<td>Both: 35.5%</td>
<td>1.2 mg</td>
<td>18 weeks</td>
<td>Both's BMI 20 k</td>
<td>Single center randomized, placebo controlled trial</td>
<td>Analysis of covariance</td>
<td>35.2 (5.2%)</td>
<td>28 weeks</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>
Results and Discussion


An extensive study was designed more than a decade ago with 564 participants; participants were randomly allocated to receive liraglutide treatment of 20-weeks duration. The dose wise participant detail was explained in Table 1. The study participants were randomly assigned to liraglutide 1.2, 1.8, 2.4 or 3.0 mg of n= 95, 90, 93, 93 respectively, and placebo n=98 by one daily, evening subcutaneous injectable administration. The starting dose was 0.6mg daily and escalated weekly. The comparator group (n=95) received orlistat capsules 3X120 mg, orally. Out of 564, 472 (84%) were completed the trial, 03 participants were also excluded from 1•2 mg, 2•4 mg, and 3•0 mg liraglutide doses due to baseline data missing of body weight, 3 due to noncompliance of criteria, 12 had week 20 missing assessment, 7 with treatment compliance concerns, and 01 due to drug dispensing error. The liraglutide group (all doses) reported significant weight loss from 4•8 to 7•2 kg. About 224 (61%) of liraglutide group participants lost > 5% of their body weight, liraglutide 3•0 mg significantly reduced >5% body weight in comparison with orlistat. The adverse events frequency was higher with a high dose of liraglutide. Liraglutide1•8 mg, 2•4 mg, and 3•0 mg reported more adverse events than liraglutide 1•2 mg, placebo, and orlistat. About 10% participants from each treatment group experienced adverse events. Gastrointestinal events, Nausea, Constipation, Diarrhea, and vomiting were the most common ones. Most events were transient, mild, or moderate. The frequency of events increased with dose intensity. More than 80% of nausea complaints, and 50% of vomiting episodes were reported in the first 4 weeks of treatment during dose adjustment. Eight individuals withdrew from the study due to nausea and five because of vomiting. Nine participants had serious adverse episodes. Psychiatric events like insomnia, depressed mood, and nervousness were more often reported in 6 individuals of liraglutide 2•4 mg. Depression and anxiety were reported by 2 individuals in each group.

Other adverse events were General disorders and administration-site conditions like fatigue, Gastroenteritis, Nasopharyngitis, Injury, poisoning, and procedural complications, Metabolism and nutrition disorders, Musculoskeletal and connective-tissue disorders, Nervous system disorders, Headache, Skin and subcutaneous-tissue disorders. No case of pancreatitis was reported. The serious adverse events in each individual and withdrawal due to liraglutide 3.0 mg were cholelithiasis, and acute pancreatitis after 299 days, anaphylactic reaction after 692 days, and atrial fibrillation after 707 days. Liraglutide 1.8mg, serious adverse events and withdrawal was reported because of Breast cancer after 465 days and prostate cancer after 94 days of therapeutic administration. Liraglutide 2•4 mg reported intestinal adenocarcinoma after 410 days, uterine leiomyoma after 219 days.

This 2 year study concluded Liraglutide as a sustainable therapeutic in weight reduction, well-tolerated, and beneficial for cardiovascular health.

Safety and Efficacy Evaluation of obesity drugs including Liraglutide in nondiabetic, severely obese individuals [13]

This 26 week randomized study was started with 474 participants and completed with 444. The study was categorized into 5 groups including double-blind placebo, JNJ-64565111 5.0 mg, JNJ-64565111 7.4 mg, JNJ-64565111 10.0 mg, and open-label Liraglutide 3.0 mg. The starting dose of Liraglutide was 0.6mg/per day, and titrated gradually to 1.2, 1.8, 2.4, and 3.0 till week 5 and then continued to 3.0 mg dose till week 26. The defined outcome was ≥ 5% reduction of body weight which was awaited.

The 119 reported adverse events associated with liraglutide 3.0mg were seen in 81 individuals, mostly minor to moderate, included gastrointestinal disorders, general disorders, and infections. The serious adverse events associated with mortality risk were seen in 4 (3.36%) individuals. Those reported were Myocardial Infarction, acute pancreatitis, Biliary Colic, Cholelithiasis, and major depression.

Effect of liraglutide 3.0 mg in obese individuals having moderate or severe obstructive sleep apnea [14]

A randomized double-blind control trial with liraglutide 3.0 mg was designed in 359 nondiabetic, obese individuals having moderate or severe obstructive sleep apnea. The primary outcome was an improvement in apnea-hypopnea index (AHI) and also it evaluated the weight loss by 32 weeks duration.
of liraglutide 3.0mg administration. The starting dose of liraglutide was 0.6 mg/day and increased weekly to 3.0mg, and then maintained for 28 weeks. This study reported significantly greater improvement in AHI as compared to placebo. Weight reduction was also significantly seen in the liraglutide group i.e. 46.3% participants lost more than 5% of their body weight. A noteworthy improvement was also reported in Glycemic control and cardiometabolic indices.

Out of 359, 276 completed the study, 134 (74%) from liraglutide group and 142 (79%) from placebo.

More individuals reported adverse events with the liraglutide group i.e. 80.1%, Liraglutide group also had a higher withdrawal rate due to adverse events than placebo 12% vs. 3%. Gastrointestinal mild to moderate adverse events were the most common. Serious adverse events were Angina pectoris, Anxiety, Cholelithiasis, Coronary revascularization, Dehydration, Depression-suicidal, Oropharyngeal swelling, Pneumonia, Procedural pain, Sinus arrest, Sleep apnea syndrome, and Spinal fracture. This study concluded liraglutide 3.0mg is a significantly superior therapeutic than placebo or lifestyle modification alone, and pronounced weight loss resulted in AHI reduction, improved cardiovascular health, and improved systolic blood pressure.

Liraglutide 3.0mg in Weight Management [15]
A 56-week double-blind trial was designed with 3,731 participants, 2,487 for liraglutide 3.0 mg with lifestyle modification and 1,244 for placebo plus lifestyle intervention, negative for type 2 diabetes with 27-30 BMI. The evaluation was done every 2 weeks till week 8, then on every 4 weeks evaluation until weeks 50, 56, 58, 60, 64, 68, and 70. A total of 71.9% (n=1789) of liraglutide group individuals and 64.4% (n=801) of the placebo group completed the 56 weeks study. A large number of liraglutide group individuals withdrew due to adverse events i.e. 246 of 2,487 (9.9%) participants, and 23 of 2,487 (0.9%) due to ineffective therapy. 264 participants out of 2,487 (10.6%) withdrew their consent. After 56 weeks of evaluation, liraglutide individuals lost body weight of 8.4±7.3 kg and maintained it throughout the 56 weeks of assessment. 63.2% of patients lost around 5% of their weight, and 92% of the total liraglutide group reportedly lost body weight. Other glycemic, cardiometabolic variables and indices were significantly positive; the liraglutide group reduced ≥5% of weight loss during 4-12 weeks duration. Immediately after ≥5% of weight loss participants were taken up for low-calorie diet - LCD and encouraged to reduce ≥5% of initial weight loss during 4-12 weeks duration. This study reported similar effects of liraglutide administration with prediabetes and nondiabetic individuals with significant improvement in metabolic control also. This is an exception study and was included because of comparative conclusion of liraglutide administration in prediabetes and nondiabetic individuals.

Three months liraglutide 1.8mg treatment in obese, in non-diabetic, binge eating individuals [16]
Forty-two obese binge eater individuals were randomly categorized: 21 participants in liraglutide 1.8mg group, plus exercise, and diet; twenty one individuals in the control group – exercise and diet only, for 3 months. The assessment was done on 1, 6, and 12 week intervals. Liraglutide receiving participants reportedly had marked reduction in Binge Eating Scale (BES) from 20 to 11, weight from 94.54 ± 18.14 kg to 90.14 ± 19.70 kg, BMI from 36.15 ± 3.84 kg/m2 to 34.40 ± 4.77 kg/m2, and waist circumference from 103.9 ± 13.7 cm to 100.2 ± 14.0 cm. Overall 50% of liraglutide individuals resulted in 5% of weight reduction which also reduces cardiovascular risks. This study used Ghrelin testing as a hunger indicator which was significantly increased and ultimately reduced body weight. No adverse effects were reported in this pilot study.

Weight maintenance randomized study with liraglutide [17]
The study was conducted with 422 participants, with 40% drop out. Initially, 675 participants were screened; 551 were taken up for low-calorie diet - LCD and encouraged to reduce ≥5% of initial weight loss during 4-12 weeks duration. Immediately after ≥5% of weight loss participants were randomly allocated to liraglutide 3.0 mg daily in a 1:1 ratio of n = 212 and placebo group n = 210. Liraglutide dose initially started with 0.6 mg and escalated between 4-5 weeks and continued with 3.0 mg till 56 weeks. 53 participants were withdrawn from the liraglutide group and 64 from the placebo. 18 participants from each group were withdrawn due to adverse events. Results were significantly positive ; the liraglutide group reduced a further 6.2% (mean) body weight. 81.4% of liraglutide participants reduced ≥5% of body weight and 26.1% lost ≥10% of their body weight.

In terms of safety 91.5 vs. 88.6% of liraglutide and placebo group participants respectively reported adverse events, with more frequency of events in the liraglutide group.

Six out of eighteen withdrawals experienced serious events i.e. ischemic colitis, worsening cholelithiasis, ovarian cancer, papillary thyroid carcinoma, and bilateral breast cancer in the liraglutide group. Eleven withdrawals were
due to the most common gastrointestinal adverse events. This study also concluded liraglutide as well-tolerated and contributes well in terms of meaningful weight loss with improvement in cardiovascular risk factors.

Effects of liraglutide on metabolic activities in obese, non-diabetic adults [18]

This study was defined as the mechanism of weight loss in obese, non-diabetic individuals by Liraglutide. The first and second treatment phase was of 5 weeks with a 6-8 weeks wash off period. This was a single-institutional, randomized, double-blind placebo-controlled, crossover trial with Liraglutide 1.8 mg, 3.0 mg, and placebo per day. Out of 62 screened individuals, 42 were enrolled in the study. Weight loss was reported as a secondary outcome and the weight loss mechanism was the primary one. The 5 week mean weight loss was reported as 2.1kg and 2.5 kg with liraglutide 1.8 mg and 3.0 mg respectively. Five participants withdrew from the study, 2 because of adverse events of toe thrombosis and tooth infection. Liraglutide 1.8mg and 3.0mg both were reported as well tolerated. The reported adverse events were 90% with liraglutide 1.8 mg and 94% of liraglutide 3.0 mg, mostly gastrointestinal complaints of nausea and decreased appetite.

Low-dose liraglutide assessment in weight control among obese, non-diabetics [4]

A small scale study was conducted with 46 participants who were administered liraglutide 0.6 or 1.2 mg daily for 12 weeks. Liraglutide 1.2 mg showed better outcome with 44.4% patients with weight reduction in comparison with liraglutide 0.6mg where 32.1% patients showed weight reduction. Young age was reported as a positive factor in weight reduction, and even a low dose of liraglutide can help in weight reduction. Adverse events were not reported in this study.

Study Withdrawals due to adverse events

Gastrointestinal disorders are the most common associated adverse events with liraglutide administration. Most adverse events are self-limiting and occur mostly in the first 4-5 weeks during dose escalation, and large scale data reported these as insignificant [21, 22]. A lesser percentage of serious adverse events were reported throughout the studies. Although, these serious events are less in number participants refused to continue the study which lead to withdrawal. Figure 1, presents the overall withdrawals of all included studies among all doses of liraglutide.

Serious adverse events are always a concern associated with liraglutide consumption including pancreatitis and cancer. Although, the numbers are few they are crucial due to the nature of their severity [23]. Figure 2 (page 82) gives a comprehensive picture of all included studies and reported serious adverse events.
Obesity is a multifactorial complex disease influenced by genetic and environmental factors and pharmacological or therapeutic options plays a significant role in weight loss with minimal side effects. Liraglutide is reported as a safe, well tolerated therapeutic in all included studies with significantly improved cardiovascular health status.

Scientific studies and trials have shown liraglutide as an effective weight reducing therapeutic with limited adverse events both in diabetic and non diabetic individuals.

We need to identify the drug mechanism precisely to know the alteration in the human body in response to liraglutide administration, starting from the most common to serious adverse events as well as to identify the connection of more weight loss in individuals with absence of gastrointestinal weight loss [21]. The serious adverse events including pancreatitis, and cancer are also daunting and a specific study participant group can bear the liraglutide administration consequences [23]. Also, studies on related mortality due to severe adverse events in response to liraglutide administration are also suggested. This will help to design safer therapeutics with possibly no serious adverse effects.

References

Figure 2: Serious Adverse events reported among selected studies due to Liraglutide Administration


13. A Study to Evaluate the Safety and Efficacy of JNJ-64565111 in Non-diabetic Severely Obese Participants. ClinicalTrials.gov Identifier: NCT03486392


19. Marcio CM, Maria E de M. The burden of obesity in the current world and the new treatments available: focus on liraglutide 3.0 mg. Mancini and de Melo Diabetol Metab Syndr 2017; 9:44. DOI 10.1186/s13098-017-0242-0


