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Review Article

Liraglutide: The Promising Weight Reducing Medication. Review Article

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Abstract: Worldwide, obesity is a significant concern, affecting approximately one third of the total population. Obesity induces the major metabolic disorders: diabetes, cardiovascular disease, hypertension, fatty liver disease, and increases people's risk of stroke and even death. GLP-1 is released after meals, prolongs gastric emptying time, and mediates satiety. Liraglutide, a long-acting GLP-1 agonist, augments insulin release and is originally used for the treatment of type 2 diabetes. This medication result in weight reduction, and has been approved for the treatment of obesity. Clinical trials have revealed significant reduction in body weight and BMI at a dose of up to 3.0 mg per day. The most common adverse reactions are gastrointestinal, which often subside with time. Safety concerns regarding thyroid tumors and pancreatitis must be carefully considered before using of this agent. ***Objective:*** to review the clinical applicability, efficacy, and safety of liraglutide for weight management from phase III clinical trials. ***Methods:*** A search of the literatures was performed using terms: "liraglutide", "GLP-1 agonist", and "randomized clinical trial". Articles pertinent to the subject were reviewed and supplementary references known to the authors were included. ***Results:*** Ten randomized, placebo-controlled clinical trials of liraglutide for weight reduction were identified. In addition to life-style modification, liraglutide resulted in a 6 - 10% weight reduction compared with placebo. The most common adverse effects were gastrointestinal, early in the treatment course. Comparative data showed that weight loss with liraglutide is more than that observed with orlistat. Liraglutide 1.8 mg had shown to have cardiovascular benefit. Restrictions to clinical use as first-line medications include GIT side effects, need for injection, and the high cost. *Conclusions*: Liraglutide induces weight loss in patients with obesity. Its efficacy is comparable to other available drugs, and it offers the unique benefit of improved glycemic control. Additional studies are required to determine its long term efficacy and safety.

Keywords: GLP-1 receptor agonist, liraglutide, obesity, weight loss.

INTRODUCTION

Liraglutide Is a medication used to treat diabetes mellitus type 2 and obesity. Its effects on long term health outcomes like heart disease and life expectancy are unclear. Common side effects include low blood sugar, nausea, dizziness, abdominal pain, and pain at the site of injection ("Liraglutide Monograph for Professionals". 2019). Other serious side effects may include medullary thyroid cancer, angioedema, pancreatitis, gallbladder disease, and kidney problems (Shyangdan, D. et al.., 2011). Use in pregnancy and breast-feeding is of unclear safety. Liraglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 receptor agonist) also known as incretin mimetics ("Liraglutide Monograph for Professionals". 2019). It works by increasing insulin release from the pancreas and decreases excessive glucagon release ("Liraglutide Monograph for Professionals". 2019).

Pharmacodynamics

Liraglutide is an acylated glucagon-like peptide-1 (GLP-1) agonist, derived from human GLP-1-(7-37), and (less commonly) form of endogenous GLP-1. It reduces meal-related hyperglycemia (for 24 hours after administration) by increasing insulin secretion (only) when required by increasing glucose levels, delaying gastric emptying, and suppressing prandial glucagon secretion (Goldstein, B.J., &Mueller-Wieland, D. (14 November 2007). Liraglutide leads to insulin release in pancreatic beta cells in the presence of elevated blood glucose. This insulin secretion subsides as glucose concentrations decrease and approach euglycemia. It also decreases glucagon secretion in a glucose-dependent manner and delays gastric emptying. Unlike endogenous GLP-1, liraglutide is stable against metabolic degradation by peptidases, with a plasma half-life of 13 hours (Beglinger, C., & Degen, L. 2006). It is not so much preferred as an anti-diabetic agent, It

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may be used in those where metformin and another antidiabetic medication are not sufficient (Shyangdan, D. et al., 2011).

Over the past few years, the FDA has approved a growing list of medications for the treatment of obesity. Unlike the prior mainstay for prescription weight management, phentermine, which can only be used for a few months at a time due to concerns about abuse, many of these newer medications are approved for long-term use, aligning well with the growing recognition of obesity as a chronic illness. Interestingly, most of the drugs that have emerged onto the market do not represent novel compounds, but rather are existing drugs that have been repurposed and repackaged for the indication of weight management. These medications include Qsymia (a mix of phentermine and topiramate), Contrave (naltrexone and buproprion), and now, Saxenda (liraglutide, also marketed as Victoza for treatment of type 2 diabetes) (Bray, G. A., & Ryan, D. H. 2014; Yanovski, S. Z., & Yanovski, J. A. 2015). Liraglutide, the glucagon-like-peptide 1 (GLP-1) analogue, has an effect similar to that of GLP-1, a gut hormone that stimulates insulin secretion, inhibits pancreatic beta cell apoptosis, inhibits gastric emptying, and decreases appetite by acting on the brain's satiety centers (de Mello, A. H. et al., 2015). For several years, endocrinologists and some internists have been using liraglutide (Victoza) to help with glycemic control in diabetics, with the known benefit that, unlike some other diabetes medications, it tends to promote modest weight loss (Prasad-Reddy, L., & Isaacs, D. 2015).

Clinical Trials

The first major phase III trial to study liraglutide was conducted in patients with body mass index between 30 kg/m2 and 40 kg/m2 in 8 European countries (Astrup, A. *et al*., 2009). The trial compared the effects of four different doses of liraglutide (1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg, injected subcutaneously once daily) with placebo (once daily subcutaneous injection) and an orlistat (120mg three times a day orally) (Astrup, A. *et al*., 2009). Individuals with type 1 or 2 diabetes, major medical problems, drug induced obesity, those using other weight lowering pharmacotherapy, those enrolled in a clinical weight control study over the past 3 months, and recipients of bariatric surgery were excluded. All participants were prescribed a lifestyle intervention during the treatment period to include a 500 kcal per day energy deficit diet (based on estimated 24 hour energy expenditure) and counseling on increased physical activity using pedometers. The primary endpoint was change in body weight among the intention-to-treat (ITT) population at the end of 20 weeks. The estimated mean weight loss in the ITT population was significantly greater with all doses of liraglutide as compared with placebo (4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg for liraglutide 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg, respectively vs. 2.8 kg for placebo; $p<0.01$ for all doses). Participants receiving 2.4mg and 3.0mg liraglutide lost significantly more weight than those receiving orlistat (6.3 kg and 7.2 kg vs. 4.1 kg, $p<0.01$ for both). The most common adverse events with liraglutide 3.0mg were nausea and vomiting, occurring nine and six times more frequently than placebo, respectively. 80% of the nausea events and 50% of the vomiting events occurred during the first 4 weeks of the trial. Psychiatric disorders were slightly more frequent and mean pulse rate was slightly increased with liraglutide treatment as compared to placebo and orlistat. The result of this trial suggested the potential utility of liraglutide as a long-term weight loss agent (Astrup, A. *et al*., 2009).

The SCALE Sleep Apnea trial was a 32-week randomized, double-blind, placebo-controlled trial conducted in the United States and Canada (Blackman, A. *et al*., 2016). Individuals with a diagnosis of moderate or severe obstructive sleep apnea by poly-somnogram who were unwilling or unable to use continuous positive airway pressure (CPAP) treatment and had a BMI ≥ 30 kg/m2 were randomized in a 1:1 ratio to receive once daily subcutaneous liraglutide 3.0mg injections or placebo. Dosing followed standard protocol and both groups received counseling on lifestyle modifications. Individuals with diabetes were excluded. A sleep study was performed at screening, at 12 weeks, and at the end of the trial at 32 weeks. The primary endpoint was change in the apnea-hypopnea index (AHI). Secondary outcomes included changes in body weight and glycemic control. Patients randomized to liraglutide 3.0mg group had a significantly greater reduction in the mean body weight (5.7% versus 1.6%), had a greater proportion of patients who lost at least 5% (46.3% versus 18.5%) and 10% (23.4% versus 1.7%) of the initial body weight as compared to placebo ($p<0.0001$ for all three).

Weight Loss with Liraglutide 3.0 Mg Versus Placebo For Individuals Who Adhere To The Trial Drug: A Secondary Analysis From SCALE IBT (Jena, S.T.PhD. *et al*., 2019).

In this pre-specified secondary analysis, the researchers aimed to determine the expected effect of liraglutide 3.0 mg on weight loss, as compared to placebo, if all randomized individuals had adhered to study drug for 56 weeks. A total of 282 individuals with obesity (BMI ≥30 kg/m^2) were randomized in a 1:1 ratio to 56 weeks of IBT combined with daily injections of either liraglutide 3.0 mg or placebo. The estimated placebo-subtracted weight loss for liraglutide at week 56 was approximately 4.6% in medication-adherent individuals . This finding is an important supplement to the study's primary outcome and can inform practitioners' expectations when prescribing liraglutide 3.0 mg in combination with IBT for 56 weeks (Jena, S.T.PhD. *et al*., 2019).

Another randomized double-blind placebo-controlled trial to evaluate the efficacy of liraglutide for weight loss in a group of non-diabetic patients with obesity, that was funded by NovoNordisk, the pharmaceutical company that manufactures liraglutide, took place across 27 countries in Europe, North America, South America, Asia, Africa and Australia (Lewis, K. 2015). Participants were 18 years or older, with a BMI of 30 kg/m ^{2} (or 27 kg/m ^{2} with hypertension or dyslipidemia). Patients with diabetes, those on medications known to induce weight gain (or loss), those with history of bariatric surgery, and those with psychiatric illness were excluded from participating. Patients with pre-diabetes were not excluded.

Participants were randomized (2:1 in favor of study drug) to liraglutide or placebo, stratified according to BMI category and pre-diabetes status. They were started at a 0.6–mg dose of medication and up-titrated as tolerated to a dose of 3.0 mg over several weeks. All received counseling on behavioral changes to promote weight loss. Participants were then followed for 56 weeks. A small subgroup in the liraglutide arm was randomly assigned to switch to placebo after 12 weeks on medication to examine for durability of effect of medication, and to evaluate for safety issues that might occur on drug discontinuation.

This study focused on 3 primary outcomes: individual-level weight change from baseline, group-level percentage of participants achieving at least 5% weight loss, and percentage of participants with at least 10% weight loss, all assessed at 56 weeks. Secondary outcomes included change in BMI, waist circumference, markers of glycemia (hemoglobin A1c, insulin level), markers of cardiometabolic health (blood pressure, lipids, CRP), and health-related quality of life (using several validated survey measures). Adverse events were also assessed.

The trial enrolled 3731 participants, 2487 of whom were randomized to receive liraglutide and 1244 of whom received placebo. The groups were similar on measured baseline characteristics, with a mean age of 45 years, mostly female participants (78.7% in liraglutide arm, 78.1% in placebo), and the vast majority of participants identified as "white" race/ethnicity (84.7% in liraglutide, 85.3% in placebo). Mean baseline BMI was 38.3 kg/m ^{2} in both groups. Although overweight patients with BMI 27 kg/m ^{2} or greater were included, they represented a small fraction of all participants (2.7% in liraglutide group and 3.5% in placebo group). Furthermore, although patients with overt diabetes were excluded from participating, over half of the participants qualified as having pre-diabetes (61.4% in liraglutide group, 60.9% in placebo group). Just over one-third (34.2% of liraglutide group, 35.9% placebo) had hypertension diagnosed at baseline.

Liraglutide participants lost significantly more weight than placebo participants at 56 weeks (mean [SD]: **8.0** [6.7] kg vs. **2.6** [5.7] kg). Similarly, more patients in the liraglutide group achieved at least 5% weight loss (63% vs. 27%), and 10% weight loss (33.1% vs. 10.6%) than those taking placebo. When subgroups of patients were examined according to baseline BMI, the investigators suggested that liraglutide appeared to be more effective at promoting weight loss among patients starting below 40 kg/m ^{2}. Hemoglobin A1c dropped significantly more (–0.23 points, $P < 0.001$) among liraglutide participants than among placebo participants. Similarly, fasting insulin levels dropped by 8% more ($P < 0.001$) in the liraglutide group at 56 weeks. In keeping with the greater weight loss, markers of cardiometabolic health also improved to a greater extent among liraglutide participants, with larger decreases in blood pressure (SBP –2.8 mm Hg lower in liraglutide, $P < 0.001$), and LDL (–2.4% difference, $P = 0.002$), and a larger increase in HDL (1.9% difference, $P = 0.001$).

Quality of life scores were higher for liraglutide participants on all included measures except those related to side effects of treatment, where placebo participants reported lower levels of side effects. The most common side effects reported by liraglutide participants related to GI upset, including nausea (40%), diarrhea (21%), and vomiting (16%). More serious events, including cholelithiasis (0.8%), cholecystitis (0.5%), and pancreatitis (0.2%), were also reported. Somewhat surprisingly, although liraglutide is also used to improve glycemic control in diabetics, rates of reported spontaneous hypoglycemia were fairly low in the liraglutide group (1.3% vs. 1.0% in placebo).

In another large multicenter trial, Pi-Sunyer *et al* evaluated the efficacy of liraglutide at a 3.0 mg daily dose for weight management. The trial utilized a strong study design, with double blinding, randomization of a subgroup for early discontinuation (to evaluate for weight regain and stopping-related side effects), and, importantly, the intervention for both groups also included a behavior change component. Patients were followed for 56 weeks on the medication, making the "intervention" phase of the study longer than what has been done in many diet trials. Testing for a long-lasting impact on weight, and at the same time attempting to quantify risks associated with longer-term use of a medication, was an important contribution for this study given that liraglutide is being marketed for long-term use (Pi-Sunyer, X. *et al.*, 2015). Patients without diabetes were enrolled in the trial if BMI was ≥30 (or ≥27 with other comorbidities). In a 2:1 ratio, patients were

randomized to receive liraglutide (n = 2487) or placebo (n = 1244). The dose of liraglutide was initiated at 0.6 mg subcutaneously daily and titrated up 0.6 mg weekly to the target dose of 3.0 mg daily. Both groups received counseling on lifestyle modifications.

After 56 weeks, patients in the liraglutide group lost 8.4 kg ± 7.3 kg while patients in the placebo group lost 2.8 kg ± 6.5 kg from baseline ($p < 0.001$ vs placebo). After a year on liraglutide, participants in that group had lost around 6 kg more, on average, than those using placebo, and had achieved greater improvements cardiometabolic risk markers, with a much lower risk of developing diabetes. The percentage of patients who lost at least 5% of their body weight from baseline was 63.2% in the liraglutide group vs. 27.1% in the placebo group ($p < 0.001$ vs placebo). Likewise, 33.1% of patients in the liraglutide group vs 10.6% of patients in the placebo group lost at least 10% of their body weight from baseline ($p < 0.001$). The rate of GI side effects (nausea, vomiting, diarrhea) in liraglutide participants was fairly high, within the first 4 - 8 weeks of treatment, and it is worth considering whether the side effects themselves could have been driving some of the weight loss observed in that group. Based on the results of this trial, the authors concluded liraglutide 3.0 mg once daily, in combination with diet and exercise, produced clinically meaningful weight loss in obese patients without diabetes.

A small study involving 328 patients, aimed to assess the effect of liraglutide on body weight and waist circumference in overweight and obese Chinese patients with T2DM. In this open-label study, patients received up to 1.8 mg daily of liraglutide over 24 weeks. The primary endpoints were defined as changes in body weight, BMI, and waist circumference to height ratio (WHR) from baseline. After 24 weeks of treatment, significant reductions in all primary outcomes were observed. The authors compared their results to clinical trials conducted in Western countries and concluded that liraglutide is more effective in Chinese patients than Western patient populations. It is important to note here, the trials being compared were not designed to evaluate weight loss as a primary outcome and thus this conclusion warrants further investigation (Feng, P. *et al*., 2015).

A smaller trial involving 44 obese binge-eaters aimed to evaluate the efficacy of liraglutide 1.8 mg daily for 12 weeks. Subjects were randomized to receive liraglutide 1.8 mg plus diet and exercise or diet and exercise alone. Subjects were excluded if they were taking medications which affect weight or appetite and if they had diabetes, impaired glucose tolerance, or cardiovascular disease. Liraglutide treatment resulted in significant decreases in BMI, and waist circumference from baseline as compared in subjects in the control group. The investigators concluded that 12 weeks of liraglutide treatment in non-diabetic binge-eating patients resulted in significant improvements in body weight (Robert, S. A. *et al*., 2015).

An observational study reported the results from 84 overweight or obese women with polycystic ovary syndrome (PCOS) who were treated with up to 1.8 mg of liraglutide daily for at least 4 weeks (Rasmussen, C. B., & Lindenberg, S. 2014). Patients were included in the study if they had failed to lose any weight despite therapy with metformin and lifestyle interventions for 6 months. The primary endpoints were change in body weight and BMI from baseline. Mean body weight at baseline was 98.9 kg and the mean duration of treatment with liraglutide was 27.8 weeks. Results of this study showed a mean weight loss of 9kg (95% CI 7.8 - 10.1; $p < 0.0001$) and a mean change in BMI of 3.2 kg/m2 (95% CI 2.8 - 3.6; $p < 0.0001$) from baseline. When evaluating these parameters in patients who were treated for ≥20 weeks, the mean weight loss and change in BMI compared to baseline were even greater. Based on the results of this study, the authors concluded liraglutide may be an effective adjunct to metformin, diet, and exercise in overweight and obese women with PCOS.

The efficacy of liraglutide was evaluated in another trial of 84 overweight or obese women who had a diagnosis of PCOS (Jensterle, M. *et al*., 2015). In this 12 week trial, 32 obese women with newly diagnosed PCOS were randomized to receive metformin 1000 mg twice daily or liraglutide 1.2 mg daily. Changes in BMI, body weight, waist circumference, and body fat mass were the primary endpoints. After 12 weeks, significant changes in BMI, body weight, waist circumference, and body fat mass were experienced by patients in both groups compared to baseline. Adverse effects reported by both groups were gastrointestinal in nature with nausea and diarrhea most commonly reported. Based on the results of this study, the investigators concluded short term treatment with liraglutide was associated with significant weight loss in obese women with PCOS (Jensterle, M. *et al*., 2015).

The efficacy of liraglutide in reducing A1C and weight was investigated in a prospective, observational study of Arab patients with T2DM (Bashier, A. M. *et al*., 2015).This study was conducted at 3 centers in Dubai, and included all adult patients with T2DM between 18 - 70 years of age who received a prescription for liraglutide. The dose of liraglutide was initiated at 0.6 mg and titrated to 1.2 mg or 1.8 mg daily as tolerated. The primary endpoints were defined as change in weight and A1c from baseline to 6 months. The mean change in body weight from baseline to 6 months was 2.5% ($p < 0.001$). In addition, the mean A1c decreased from 8.3% at baseline to 7.6% after 6 months ($p < 0.001$). Based on these results, the

investigators concluded liraglutide as add on therapy for diabetes, produced significant reductions in weight and A1c in this Arab population (Bashier, A. M. *et al*., 2015).

Comparison of Liraglutide with Other Weight Loss Agents

Currently there are four (other than liraglutide) FDA approved long-term weight loss agents – orlistat, lorcaserin, and fixed-dose combinations of phentermine/topiramate and naltrexone/ bupropion. All the above mentioned FDA approved weight lowering agents have been shown to cause clinically significant weight loss of at least 5% of initial body weight when used as an adjunct to lifestyle interventions. However, the degree of weight loss over a period of 1 year is variable. A recent network meta-analysis comparing the effectiveness of these five medications demonstrated that liraglutide was one of two medications associated with the highest odds of achieving at least 5% weight loss as compared with placebo (Khera, R. *et al*., 2016). Liraglutide had higher odds of achieving at least 5% weight loss at one year in clinical trials, than with lorcaserin or orlistat, similar odds as compared with naltrexone/ bupropion, and slightly lower odds as compared with phentermine/topiramate. In clinical trials, the likelihood of discontinuation of liraglutide due to adverse events were similar as compared with phentermine/topiramate and naltrexone/bupropion but were higher when compared with lorcaserin, orlistat, or placebo (Khera, R. *et al*., 2016).

Guidelines from the American Heart Association/- American College of Cardiology/The Obesity Society recommend using a multifactorial approach to manage obesity (Jensen, M. D. *et al*., 2014). This includes initiation of comprehensive lifestyle intervention programs and pharmacotherapy in individuals with BMI ≥ 30 kg/m2 or ≥ 27 kg/m2 with comorbid conditions like type 2 diabetes, hypertension, dyslipidemia, or obstructive sleep apnea if lifestyle modification alone is not effective (Apovian, C. M.*et al*., 2015). Liraglutide may be a particularly effective choice among obese patients with type 2diabetes, and can be considered for those at high risk for cardiovascular disease given a beneficial signal in cardiovascular outcomes seen in the 1.8mg formulation in a diabetes population; however the effects of the 3.0mg formulation on cardiovascular morbidity and mortality need to be more investigated. It is important to note that the safety and efficacy of co-administration of liraglutide with other weight loss agents has not been studied and it is not known whether the effects may be synergistic or if side effects would limit concomitant use. Further studies of pharmacological combination therapies may be warranted. Additional important considerations in the application of liraglutide to clinical weight management in the context of currently available agents include its high cost, injectable delivery system, and requirement for dose titration.

CONCLUSION

Liraglutide given at a dose of 3.0 mg daily, along with lifestyle advice, produces clinically significant weight loss and improvement in glycemic and cardiometabolic parameters that is sustained after 1 full year of treatment. Liraglutide may be a particularly effective choice among obese patients with type 2diabetes, and can be considered for those at high risk for cardiovascular disease given a beneficial signal in cardiovascular outcomes seen in the 1.8mg formulation in a diabetes population. Its efficacy is comparable to other available drugs, and it offers the unique benefit of improved glycemic control. Additional studies are required to determine its long term efficacy and safety.

REFERENCES

1. "Liraglutide Monograph for Professionals". *(2019). Drugs.com. American Society of Health-System Pharmacists*. Retrieved 23 March.
2. Shyangdan, D., Cummin,s E., Royle, P., & Waugh, N. (May 2011). "Liraglutide for the treatment of type 2 diabetes". *Health Technol Assess. 15 Suppl 1: 77–86.*
3. Goldstein, B.J., Mueller-Wieland, D. (14 November 2007). Type 2 Diabetes: Principles and Practice (2nd Ed.). *CRC Press. ISBN 978-0-8493-7958-1. Retrieved 17 January 2015.*
4. Beglinger, C., & Degen, L. (2006). Gastrointestinal satiety signals in humans—physiologic roles for GLP-1 and PYY? *Physiology & behavior*, *89*(4), 460-464.
5. Shyangdan, D., Cummins, E., Royle, P., & Waugh, N. (May 2011). "Liraglutide for the treatment of type 2 diabetes". *Health Technol Assess*. 15 Suppl 1: 77–86.
6. Bray, G. A., & Ryan, D. H. (2014). Update on obesity pharmacotherapy. *Annals of the New York Academy of Sciences*, *1311*(1), 1-13.
7. Yanovski, S. Z., & Yanovski, J. A. (2015). Naltrexone extended-release plus bupropion extended-release for treatment of obesity. *Jama*, *313*(12), 1213-1214.
8. de Mello, A. H., Prá, M., Cardoso, L. C., de Bona Schraiber, R., & Rezin, G. T. (2015). Incretin-based therapies for obesity treatment. *Metabolism*, *64*(9), 967-981.
9. Prasad-Reddy, L., & Isaacs, D. (2015). A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. *Drugs in context*, *4*.
10. Astrup, A., Rössner, S., Van Gaal, L., Rissanen, A., Niskanen, L., Al Hakim, M., ... & NN8022-1807 Study Group. (2009). Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *The Lancet*, *374*(9701), 1606-1616.

11. Blackman, A., Foster, G. D., Zammit, G., Rosenberg, R., Aronne, L., Wadden, T., ... & Mignot, E. (2016). Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. *International journal of obesity*, *40*(8), 1310.
12. Jena, S.T.PhD., Thomas, W.PhD., Daniel, S.MD., Michael, L.MD.PhD., Pernille, A. MD.PhD., Lars, E,PhD., Domenica, R.MD. (2019), *Journal of the Endocrine Society, 3(1), April-May*.
13. Lewis, K. (2015). Liraglutide Produces Clinically Significant Weight Loss in Nondiabetic Patients, But At What Cost?. *Journal of Clinical Outcomes Management*, *22*(9).
14. Pi-Sunyer, X., Astrup, A., Fujioka, K., Greenway, F., Halpern, A., Krempf, M., ... & Wilding, J. P. (2015). A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *New England Journal of Medicine*, *373*(1), 11-22.
15. Feng, P., Yu, D. M., Chen, L. M., Chang, B. C., Li, S. Y., Zhu, M., ... & Lin, J. N. (2015). Liraglutide reduces the body weight and waist circumference in Chinese overweight and obese type 2 diabetic patients. *Acta Pharmacologica Sinica*, *36*(2), 200.
16. Robert, S. A., Rohana, A. G., Shah, S. A., Chinna, K., Mohamud, W. N. W., & Kamaruddin, N. A. (2015). Improvement in binge eating in non-diabetic obese individuals after 3 months of treatment with liraglutide–A pilot study. *Obesity research & clinical practice*, *9*(3), 301-304.
17. Rasmussen, C. B., & Lindenberg, S. (2014). The effect of liraglutide on weight loss in women with polycystic ovary syndrome: an observational study. *Frontiers in endocrinology*, *5*, 140.
18. Jensterle, M., Kravos, N. A., Pfeifer, M., Kocjan, T., & Janez, A. (2015). A 12-week treatment with the long-acting glucagon-like peptide 1 receptor agonist liraglutide leads to significant weight loss in a subset of obese women with newly diagnosed polycystic ovary syndrome. *Hormones*, *14*(1), 81-90.
19. Bashier, A. M., Hussain, A. A. K. B., Abdelgadir, E. I. E., Eltinay, A. T., Thadani, P., Abdalla, M. E., ... & AlAwadi, F. F. (2015). Liraglutide effect in reducing HbA1c and weight in Arab population with type2 diabetes, a prospective observational trial. *Journal of Diabetes & Metabolic Disorders*, *14*(1), 48.
20. Khera, R., Murad, M. H., Chandar, A. K., Dulai, P. S., Wang, Z., Prokop, L. J., ... & Singh, S. (2016). Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. *Jama*, *315*(22), 2424-2434.
21. Jensen, M. D., Ryan, D. H., Apovian, C. M., Ard, J. D., Comuzzie, A. G., Donato, K. A., ... & Loria, C. M. (2014). 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Journal of the American college of cardiology*, *63*(25 Part B), 2985-3023.
22. Apovian, C. M., Aronne, L. J., Bessesen, D. H., McDonnell, M. E., Murad, M. H., Pagotto, U., ... & Still, C. D. (2015). Pharmacological management of obesity: an Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, *100*(2), 342-362.