Obesity Facts

Review Article

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Clinical Impact of Glucagon-Like Peptide-1 Receptor Analogs on the Complications of Obesity

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Abstract
Background: Obesity is a chronic disease associated with increased morbidity and mortality due to its complications. The aims of obesity treatment are primarily to accomplish weight loss, and prevention or treatment of its complications. Lifestyle changes along with behavioral therapy constitute the first-line treatment of obesity followed by pharmacotherapy. Glucagon-like peptide receptor analogs (GLP-1 RAs) are among the approved pharmacotherapy options. Their central effect on suppressing appetite results in considerable weight loss. However, their effect on the complications of obesity has not been very well recognized. This review aims to analyze the effects of GLP-1 RAs on the complications of obesity, as diabetes mellitus, hypertension, nonalcoholic steatohepatitis (NASH), cardiovascular diseases, polycystic ovary syndrome, infertility, obstructive sleep apnea (OSA), osteoarthritis, cancer and central nervous system problems. ***Summary:*** Data from preclinical studies and clinical trials have been thoroughly evaluated. Effects regarding the complications as far as the scope of this review have covered can be summarized as blood glucose lowering, blood pressure lowering, resolution of NASH, improving major cardiovascular events, improving fertility and sex hormone levels, and improvement in OSA symptoms and in cognitive scores. Although the mechanisms are not fully elucidated, it is clear that the effects are not solely due to weight loss, but some pleiotropic effects like decreased inflammation, oxidative stress, and fibrosis also play a role in some of the complications. ***Key Messages:*** Treating obesity is not only enabling weight loss but ameliorating complications related to obesity. Thus, any antiobesity medication has to have some favorable effects on the complications. As far as the GLP-RA's analogs are concerned, there seems to be an improvement in many of the complications regardless of the weight loss effect of these medications.

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Introduction

Obesity is a chronic disease associated with multiple complications [1] that lead to increased morbidity and mortality [2]. Main aims of treatment of obesity are weight loss, weight maintenance, prevention of weight regain, and prevention or treatment of its complications. Lifestyle changes along with behavioral changes form first-line treatment of obesity followed by pharmacotherapy, when lifestyle changes do not suffice. Among medical therapeutics, glucagon-like peptide receptor analogs (GLP-1 RAs) have started to play an important role. Liraglutide (LIRA), followed by semaglutide (SEMA), has Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for obesity treatment. GLP-1 RAs act through hypothalamic hunger and satiety centers by decreasing appetite, along with delaying gastric emptying and increasing insulin secretion. Much emphasis has been previously made on the effects of GLP-1 RAs on weight loss, but evidence about the effect on complications is relatively scarce. This review aims to put together data about how GLP-1 RAs are effective on complications of obesity, and possible mechanisms playing a role other than weight loss.

GLP-1 is expressed in L cells in the gastrointestinal tract, alpha pancreatic cells, and in the brain [3]. GLP-1 receptor (GLP-1 R) has been identified in many tissues, with the highest expression in lung and pancreas, less expression in stomach, intestine, kidney, heart, and brain [4]. Thus, the targets of GLP1-RAs are far beyond the prespecified effects. Type 2 diabetes mellitus (T2DM), hypertension (HT), cardiovascular disease, nonalcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), infertility, obstructive sleep apnea (OSA) syndrome, osteoarthritis (OA), cancers and central nervous system disorders are among major complications of obesity.

Type 2 Diabetes Mellitus

The risk of developing T2DM increases with adiposity and increasing body mass index (BMI) [5]. There is a common pathophysiological pathway between these diseases, possibly through compromised incretin function [6]. LIRA is an agent that is initially approved for the treatment of T2DM; thus, the data about LIRA come mostly from clinical trials with diabetes.

Clinical Data

GLP-1RAs improved glycemic profile and decreased body weight (BW) compared with placebo [7]. LIRA (3.0 mg) caused more weight loss among overweight and obese participants with T2DM than placebo and LIRA 1.8 mg [8]. Prediabetic subjects who continued on LIRA 3.0 mg or placebo for two more years showed a decreased risk of diabetes in the LIRA group (HR, 0.21; 95% CI, 0.13–0.34; $p < 0.001$). This advantage remained after a 12-week follow-up after discontinuation of treatment. Furthermore, LIRA enabled regression from prediabetes to normoglycemia more when compared to placebo (OR, 3.6; 95% CI, 3.0–4.4; $p < 0.001$). Reduction of BW was more prominent in the group that remained normoglycemic, indicating that BW reduction plays a primary role in delaying T2DM [9]. Additionally, GLP-1 preserves beta-cells [10–12]. Taken together, improved beta-cell function and insulin resistance (IR) followed by LIRA-induced BW reduction prevent diabetes in high-risk patients [9].

Other GLP-1 RAs include exenatide twice daily (EXE BID) and EXE QW (Bydureon) once weekly, lixisenatide (Lyxumia) once daily, dulaglutide (Trulicity) once weekly, and albiglutide (Tanzeum or Eperzan) once weekly [13]. The data comparing GLP-1 RAs head to head are limited in terms of weight loss and HbA1c reduction [13]. Studies suggest a similar HbA1c-lowering effect between lixisenatide and EXE BID, while showing more weight loss with EXE BID. Albiglutide was less effective at both lowering HbA1c and achieving weight loss compared with LIRA. Dulaglutide once weekly was more effective than EXE BID and was noninferior to LIRA at HbA1c reduction. Weight loss was similar between dulaglutide and EXE BID but was greater with LIRA than dulaglutide [14] (Fig. 1).

GLP-1 RAs improved glycemic profile and decreased BW compared with placebo [7]. A systemic review of GLP-1 RAs in T2DM showed that LIRA was as efficient as dulaglutide, and EXE and albiglutide were inferior to LIRA in achieving glycemic goals [15].

SUSTAIN 1-6 trials assessed the glucose-lowering efficacy of SEMA compared to placebo, DPP-4 inhibitor, GLP-1 RAs, and long-acting insulin. A significant benefit of SEMA in glucose lowering and weight reduction was observed [16–21]. SUSTAIN-7 showed a significant reduction in mean HbA1C and BW in SEMA than dulaglutide [22] SUSTAIN 8–10 clinical trials confirmed the efficacy of SEMA in terms of glucose control without raising any new safety concerns [23–25]. In the PIONEER trials, oral SEMA provided significantly better efficacy

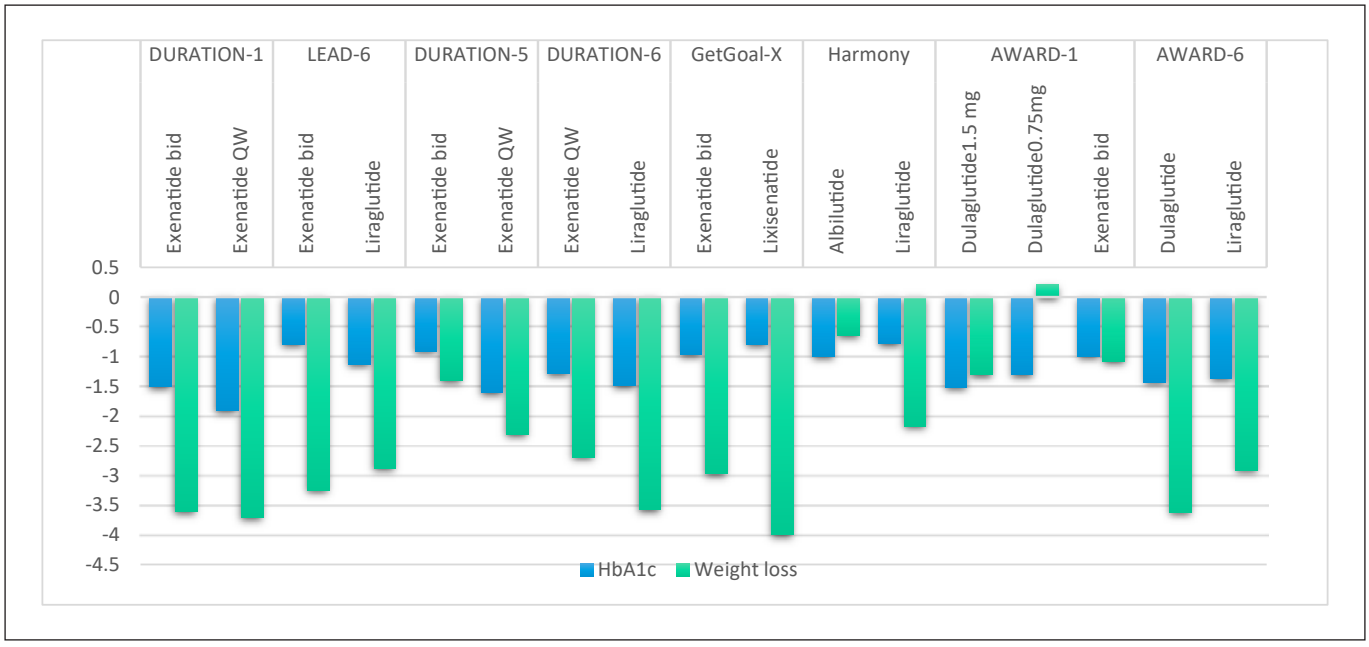


Fig. 1. Studies comparing GLP-1 RAs in terms of weight loss and HbA1c reduction [14].

than placebo and DPP-4 inhibitor (sitagliptin), SGLT-2 inhibitors (empagliflozin), as well as LIRA and dulaglutide [26]. Provided that SEMA 1.0 mg has the greatest weight loss effect in patients with type 2 diabetes, a higher dose of 2.4 mg for weight management in adults with overweight or obesity and type 2 diabetes was investigated. The clinically significant weight loss was accompanied by an HbA1c reduction with SEMA 2.4 mg, than SEMA 1.0 mg, and placebo [27].

Drug Effect

Since the fact that while the glucose-lowering effect is comparable among different agents in patients with DM, the amount of weight loss seems to be different. This may be a clue as to the mechanism of diabetes control is through mostly the release of insulin, decreased glucagon secretion, and delayed gastric emptying, instead of weight loss. In the case of prediabetes or IR, the prevention of diabetes seems to be through weight loss.

Hypertension

Animal models of HT, such as salt-sensitive Dahl rats, salt-sensitive obese db/db mice, and chronic infusion of GLP-1 have decreased the incidence of HT [28, 29].

Clinical Data

Antihypertensive effects of GLP-1 RAs have been demonstrated in several clinical trials. There seems to be a slight lowering of blood pressure (BP) (2–6 mm Hg from baseline) with GLP RAs [30–35]. Despite the fact that GLP1 RAs decreased BP in the long run, short-term treatment has been shown to increase in both systolic and diastolic BP, possibly due to increased heart rate and cardiac output at the beginning of therapy [36].

Drug Effect

The hemodynamic effects of GLP RAs in kidney have been postulated to be through two different mechanisms: through decreased proximal tubular sodium resorption, leading to lower glomerular filtration rate (GFR) and renal blood flow and through dilatation of afferent arteriole, which has a role in increasing GFR and renal blood flow. Type of GLP-1 agonist, dose, baseline GFR, and the metabolic state of the patient may determine which mechanism predominates [36]. There have been many animal and human data demonstrating that natriuresis may be a predominant mechanism. Studies in mice have demonstrated that the increase in atrial natriuretic peptide (ANP) resulted in natriuresis in mice [37]. Similarly, a study in patients with T2DM and HT has also showed that natriuresis increases as a result of the increase in

ANP with LIRA treatment [38]. In patients with obesity, GLP-1 infusion has resulted in an increase in urinary Na excretion, along with a decrease in urinary H+ secretion [39]. Another postulated mechanism is antagonization of the effect of angiotensin II, observed in preclinical studies [37, 40]. Clinical studies show contradictory results as to levels of ANP [37, 41], while LIRA decreased the levels of angiotensin II concentration in people with T2DM [36].

The antihypertensive effects of these kinds of drugs, as demonstrated in the LEAD trials, seem to occur before any weight loss occurs [37]. It was also demonstrated in another trial that the decrease in BP was independent of the change in BMI [42]. Thus, GLP-1 RAs have a slight antihypertensive effect in the long-term use, most probably due to hemodynamic effects.

Nonalcoholic Fatty Liver Disease

Obesity has an important role in the pathophysiology of NAFLD and its prevalence increases in parallel with escalating obesity prevalence [43]. IR is a shared characteristic of T2DM and obesity and plays a key role in the pathophysiology of NAFLD. Increased lipolysis in peripheral adipose tissue due to IR causes an overwhelming free fatty acid flux toward the liver. In addition, de novo triglyceride synthesis in the liver and decreased fatty acid beta-oxidation contribute to fat accumulation in the liver parenchyma [44]. NAFLD encompasses a wide range of liver damages starting from simple steatosis to steatohepatitis (NASH) and to advanced fibrosis/cirrhosis [45]. GLP-1 RAs are one of the promising drug groups in the treatment of the NAFLD.

Beneficial effects of GLP-1 RAs have been observed in both animal models of NASH and in vitro studies. GLP-1 RAs stimulate hepatic lipid oxidation, reduce de novo lipogenesis, and improve hepatic steatosis by modulating insulin signaling pathway [46–49]. Inflammation has been also considered to play a key role in the development of NASH [44]. Published data suggest that GLP-1 RAs might affect NASH through anti-inflammatory mechanisms [50].

Clinical Data

There are many clinical trials investigating the role of GLP-1 RAs in the treatment of NAFLD [51]. Histological improvement in hepatic steatosis, necroinflammation, and fibrosis, assessed by liver biopsy, imaging modalities, changes in serum hepatic enzyme levels, noninvasive hepatic biomarkers, IR, and anthropometric measures are parameters used for diagnosis or assessing the response to treatment in NAFLD [52].

Improvement in hepatic enzymes has been reported with GLP-1 RAs [52]. Detection of reduction in hepatic steatosis by noninvasive methods such as magnetic resonance (MR) spectroscopy, MR imaging proton density fat fraction, and ultrasonography were reported in several studies investigating the efficacy of GLP-1 RAs [53, 54]. The effect of GLP-1 RAs on hepatic fibrosis is uncertain when the findings of the studies using noninvasive assessment of liver fibrosis were evaluated [55]. Fibrosis severity has been strongly implicated in the long-term prognosis of NAFLD. Transient elastography and MR elastography are new techniques determining the presence and severity of hepatic fibrosis in patients with NAFLD, noninvasively. Despite some improvements, the effect of GLP-1 RAs on hepatic fibrosis is uncertain when the results of the studies using noninvasive assessment of liver fibrosis were evaluated [55].

There are few clinical trials with biopsy-confirmed liver histological change as the primary outcome. One of the important biopsy-confirmed studies evaluating the GLP-1 RAs efficacy in treatment of NASH is the Liraglutide Efficacy and Action in NASH (LEAN) study, where 52 patients with NASH were assigned to receive LIRA or placebo for 48 weeks. Patients included in the study have a BMI ≥25 kg/m^2 and the percentage of patients with type 2 diabetes was 35% in LIRA and 31% in placebo groups. NASH resolved in 9 of 23 patients (39%) in the LIRA group compared to 2 of 22 participants (9%) in placebo group (relative risk = 4.3 [95% CI: 1.0–17.7], $p = 0.019$). Patients receiving LIRA were less likely to have progression to fibrosis than the placebo group (36 vs. 9%; RR = 0.2; 95% CI 0.1–1.0, $p = 0.04$) [56]. LIRA treatment was associated with significant reductions in BW and also had significant improvements in HbA1c compared to placebo. Changes in weight and glycemic control in patients on LIRA were not significantly different for responders (with histological improvement) and nonresponders (without histological improvement). Authors stated that the effects of LIRA are likely to be due to a combination of a direct hepatic effect (odds ratio for treatment effect adjusted for weight was 4.12 [CI: 0.66–25.8, $p = 0.131$]) and an effect on weight loss according to the post hoc logistic regression analysis.

When SEMA in doses of 0.1, 0.2, and 0.4 mg once daily was compared with placebo, NASH resolution without worsening of fibrosis was obtained in 40% of patients in the 0.1 mg group, 36% of patients in the 0.2 mg group, 59% of the patients in the 0.4 mg group, and 17% of pa-

tients in the placebo group ($p < 0.001$ for SEMA 0.4 mg vs. placebo). An improvement occurred in fibrosis stage observed in 43% of the patients in the 0.4 mg group [57]. The authors additionally reported that the primary endpoints did not change when analyzing the subset of individuals with type 2 diabetes. Changes in weight and HbA1c were −13% and −1.2% in the 0.4 mg SEMA group, respectively, but no additional analysis has been made to control changes in weight and HbA1c [57].

Drug Effect

Whether GLP-1 RAs have direct effects on pathophysiology of NASH or they affect the pathophysiology of NASH indirectly through improving weight, IR, and glycemic control is still an unanswered question. Results of the clinical trials suggest that GLP-1 RAs are effective for the improvement in hepatic enzymes and hepatic steatosis. However, their effect on hepatic fibrosis is inconclusive.

Cardiovascular Disease

Expression of GLP-1 Rs in vascular endothelium, smooth muscle cells, and cardiomyocytes suggests that these drugs may be effective in the cardiovascular system [58]. Statistically significant improvements in various cardiometabolic parameters with GLP-1 and GLP-1 RAs have been demonstrated across animal and human models [59–61].

Clinical Data

There are seven cardiovascular safety outcome trials for GLP-1 RAs in patients with T2DM: weekly exenatide (EXSCEL) [62], lixisenatide (ELIXA) [63], albiglutide (HARMONY) [64], dulaglutide (REWIND) [65], LIRA (LEADER) [66], subcutaneous SEMA (SUSTAIN-6) [21], and oral SEMA (PIONEER-6) [67]. All cardiovascular outcome studies for GLP RAs, except for EXSCEL [62], ELIXA [63], and PIONEER-6 [67] showed an improvement in major adverse cardiovascular events (first nonfatal acute myocardial infarction, nonfatal stroke, or cardiovascular death), either a significant reduction (by 12–26%) or at least a trend toward its reduction. Moreover, post hoc analyses of SCALE studies for SEMA showed a hazard ratio of 0.42 (95% CI: 0.17, 1.08) for cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke as compared with placebo [68].

In the SCALE Obesity and Prediabetes trial, LIRA treatment was associated with reductions in BW and cardiometabolic risk factors, including waist circumference (WC), systolic and diastolic BP, fasting lipid levels, and inflammatory markers, in people with obesity (PwO) and overweight [69]. These data support a role for GLP-1 RAs in reducing the cardiovascular risks in obesity.

Drug Effect

GLP-1 and GLP-1 RAs have been shown to have effects on endothelial function (vasodilation) [70, 71], on intima media thickness [72], and therefore on atherosclerosis and plaque stability [59, 61]. GLP-1 and GLP-1 RAs have been shown to improve cardiac blood supply [73], cardiac output [74], ventricular contractility [75], myocardial glucose uptake, ischemia tolerance [73, 76], left ventricular ejection fraction [77, 78], cardiac index, and pulmonary capillary wedge pressure [79] and to reduce cardiac fibrosis [80]. Weight loss seems to be an important mechanism as well.

Polycystic Ovary Syndrome

Abdominal obesity is present in approximately 20–85% of women with PCOS [81]. Both obese and lean women with PCOS have IR, which is associated with its pathogenesis [82]. Weight loss has beneficial effects on hirsutism, ovulation rates, fertility, BP, IR, and cholesterol levels in women with PCOS [83].

Clinical Data

Combined LIRA and metformin (MET) treatment resulted in a significant weight loss and a decrease in WC in obese women with PCOS [84, 85]. LIRA 1.2 mg was found to be more effective in decreasing BW than MET in subjects with severe obesity and PCOS [86]. GLP-1 RAs alone or combined with MET compared to MET alone had a better effect in terms of BMI and WC reduction in PCOS patients with overweight and obesity [87].

Combination of LIRA and MET significantly reduced androstenedione levels [84, 88]. When therapy for PCOS was switched from MET to LIRA, androstenedione levels increased significantly, most probably due to the withdrawal of MET [84]. Combining these two medications can be more effective in improving hormonal disorders in this population.

LIRA, despite weight loss, did not improve the menstrual cycle in patients with PCOS, possibly related to the small size, short duration, and low daily LIRA dose used in these studies [84, 86]. However, when used at a higher daily dose of 1.8 mg for 6 months, LIRA increased menstrual regularity significantly [89].

Drug Effect

Reduction in BW and visceral fat adiposity seem to be effective. Increasing insulin sensitivity also seems to play an important role in improving menstrual regularity and decreasing androgen levels.

GLP-1 RAs may be used effectively and safely to improve hormonal, metabolic profile and reproductive features in the treatment of PwO suffering from PCOS. These beneficial effects should be confirmed in larger multicenter long-term randomized controlled trials.

The Reproductive System

Obesity is responsible for an increased risk of infertility or lower pregnancy rate. The main mechanisms are impairment in the hypothalamic-pituitary-ovarian axis, poor oocyte quality, and increased ovarian androgen production due to IR. Excess adipose tissue enhances the aromatization of androgens to estrogen, leading to a negative feedback on hypothalamic-pituitary-ovarian axis, and decreases gonadotropin production [90]. These alterations lead to ovulatory dysfunction and menstrual disorders. Current studies focus on the role of the fertility and pregnancy outcomes of weight reduction in these patients. Obesity in men is associated with low testosterone and reduced sex hormone-binding globulin levels. Androgen is converted to estrogen via aromatization in peripheral fat tissue, leading to decrease in serum total testosterone levels. Increased estrogens decreased gonadotropin concentrations by the negative feedback effect [91].

GLP-1 has a modulatory action on hypothalamic GnRH neurons by the modulation of presynaptic GABAergic inputs and also via kisspeptin neurons [92, 93]. EXE treatment improved the quality of sperm in high-fat diet-induced obesity mice model [94]. GLP-1 RAs might impact sperm quality by triggering GLP-1 R expression in spermatozoa and by acting in Sertoli cells [95].

Clinical Data

A 12-week treatment with LIRA 1.2 mg in combination with MET was superior to MET monotherapy in increasing pregnancy rates, per embryo transfer, and cumulative pregnancy rates in PwO with PCOS [96]. A meta-analysis reported that BW loss increased total testosterone levels, and this increase was more pronounced in those who had a higher degree of weight loss [97]. Reduced BW was associated with rise in sex hormone-binding globulin levels [97]. Testosterone replacement therapy improved metabolic parameters in hypogonadal PwO [98]. Synergistic action of sex hormones and GLP-1 RAs on metabolic and hormonal conditions in these patient groups were tested. LIRA 3.0 mg or 50 mg 1% transdermal testosterone gel resulted in a significant decrease in BW, a significant recovery of hypothalamus-pituitary-testicular axis, and a significant improvement of sexual symptoms in LIRA arm during 16 weeks [99]. Adding LIRA to a combination of testosterone undecanoate and MET achieved normal serum testosterone levels and improved erectile dysfunction [28]. These effects of LIRA could be associated with weight loss or direct effects on the Leydig cells, where GLP-1 RAs were identified [100].

Drug Effect

BW reduction seems to be the predominant mechanism in these effects. Direct effects on Leydig cells, decreased aromatization of the androgens in adipose tissue, increased GnRH pulsatile release, and decreased IR seem to be the other suggested mechanisms of the effect GLP-1 RAs in the reproductive system.

Obstructive Sleep Apnea

There is a particularly high prevalence of OSA in patients with obesity and excess weight is considered to be the most important risk factor for OSA [101]. Approximately 60–70% of individuals with OSA are overweight [102, 103]. Weight loss has been shown to reduce OSA severity and improve blood oxygen saturation and sleep architecture parameters, as well as self-reported quality of life [104, 105].

Clinical Data

In the SCALE Sleep Apnea trial, PwO with moderate or severe OSA, LIRA 3.0 mg treatment has shown improvement in OSA symptoms as well as weight loss, significantly greater reductions in apnea-hypopnea index, number of apnea events per hour and improved oxygen saturation, sleep architecture, and sleep/health-related quality of life endpoints compared to placebo. In the SCALE Sleep Apnea trial, although there was a significant reduction of the number of apneic events, most patients remained still affected by OSA after LIRA treatment. During the trial, there seemed to be 5.7 ± 0.4% weight loss in a follow-up period of 32 weeks; this is a likely expected loss of BW. The unresponsiveness can be due to the majority (around 67%) of the patients having severe OSA. Besides at the end of the follow-up duration, weight loss with LIRA had not plateaued; thus, more improvements

may have been expected with a longer follow-up [106]. LIRA 3.0 mg in conjunction with a diet and exercise regimen may be useful as a weight management component of a comprehensive therapeutic approach for OSA management.

Drug Effect

The predominant mechanism of the effect of GLP-1 RAs on OSA seems to be through weight loss since the improvements of the OSA end points in this trial were related to the amount of weight loss.

Osteoarthritis

OA is the most frequent type of joint disease, associated with pain and physical disability, which primarily involves the knees [107]. The data link obesity to knee OA development [108], and the occurrence of one disease triggers the onset of the other, causing a vicious cycle [109]. Weight loss is essential for managing patients with concurrent overweight or obesity and knee OA and improves pain and function [110]. There is a lack of valid and reliable information to manage PwO and knee OA [111].

Clinical Data

LIRA 3 mg/day in this patient group induced a significant weight loss at >52 weeks but did not reduce knee pain compared with placebo [111].

Drug Effect

Further studies are required to clarify the effects of GLP-1 RAs on knee OA.

Central Nervous System Disorders

Obesity is linked to significant brain gray matter volume changes such as reductions in left and right inferior frontal gyrus, insula, left middle temporal cortex, precentral gyrus, and cerebellum [112]. Neuropathological changes observed in brains of PwO may also be linked to neuropsychiatric dysfunctions [113]. Obesity is associated with increased impulsivity, reduced cognitive flexibility, and executive functions, in addition to lower performance on memory scores [114]. Reduced psychomotor performance and speed, reduced attention and decision-making performance, but normal working memory and visuospatial abilities were reported in PwO [115]. PwO are also under a twofold increased risk of developing Alzheimer's disease compared to normal weight individuals [116]. Obesity increases the risk of ischemic stroke even in young adults [117]. PwO have increased risk of many psychiatric disorders, such as anxiety and depression [118, 119]. These associations are thought to be due to shared factors as inflammation, mitochondrial dysfunction, genetic mutations, and increased oxidative stress, in addition to comorbidities like T2DM and HT [120, 121].

GLP-1 can be produced by the nervous system cells that are microglia, astrocytes, and neurons. It has its own G protein-coupled receptors widely distributed throughout the brain, especially in areas such as ventral segmental area, nucleus accumbens, and the hippocampus [122]. When GLP-1 Rs are activated in the brain, inflammatory cytokines such as TNF-a, IL-6, and IL-10, reactive oxygen species production, and apoptotic proteins such as caspase 3 and bax are decreased, and neurotrophic factors as GDNF, VEGF, and BDNF are increased [123]. GLP-1 through these effects can decrease apoptosis, inflammation, and oxidative stress, thereby strengthening the blood-brain barrier and synapses [123].

Clinical Data

Even though research on animal models of metabolic disturbances is accumulating, the research on humans is relatively low. In a cross-sectional study including 106 patients with type 2 diabetes and 47 controls, serum GLP-1 levels were found to be protective against mild cognitive impairment detected by the MOCA test in patients with T2DM and its levels were lower in patients with mild cognitive impairment compared to controls [124]. LIRA exposure led to improved composite memory scores in PwO treated with either LIRA or lifestyle changes [125]. LIRA use for 3 months in PwO resulted in a significant improvement in memory and attention, and this improvement was correlated with the increased activity at dorsolateral prefrontal cortex and orbitofrontal cortex [126].

Neuroprotective effects of GLP-1 RAs are also being studied in patients with Alzheimer's or Parkinson's disease. Add-on LIRA for 26 weeks in Alzheimer patients did not improve patients' cognitive scores [127]. Patients with Parkinson's disease had improved motor and cognitive scores with EXE [128].

GLP-1 RAs are also used for changing the reward responses. Obesity is associated with altered central responses to palatable food and these reward-related changes are not only limited to food but also to cocaine, opioids, alcohol, etc. [122]. By changing the dopaminergic and

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Table 1. Summary of the effects and mechanisms of GLP-R analogs on complications of obesity

	Agent	Subjects	Effect	Mechanism
Type 2 DM	LIRA 3.0 mg (n = 1,505) or placebo (n = 749) (3 years follow-up)[9]	Prediabetic subjects with overweight and obesity (n = 2,254)	Decreasing risk of DM Regression to normoglycemia	Reducing BW Preserving beta cells
	SEMA 0.5 mg (n = 128) or SEMA 1.0 mg (n = 130) versus placebo (n = 129) (30-week follow-up) (SUSTAIN 1)[16]	Patients with type 2 DM, treated with only diet and exercise alone (n = 388)[16]	HbA_{1c} decreased by 1.45% with 0·5 mg SEMA; decreased by 1.55% with 1·0 mg SEMA (from baseline 8.05%) BW decreased by 3.73 kg with 0.5 mg SEMA; decreased by 4.53 kg with 1.0 mg SEMA (mean baseline BW was 91.93 kg) [16]	Stimulating insulin secretion Lowering glucagon secretion
	Once-weekly SEMA 0.5 mg (n = 288), SEMA 1.0 mg (n = 290) or once-daily sitagliptin 100 mg (n = 290) (30-week follow-up) (SUSTAIN 2)[17]	Patients with T2DM, inadequately controlled on metformin (n = 868)[17]	HbA_{1c} decreased by 1.4% with 0.5 mg SEMA; decreased by 1.7% with 1.0 mg SEMA, by 0.9% with sitagliptin (from baseline 8.1%) BW decreased by 2.9 kg with 0.5 mg SEMA; decreased by 4.2 kg with 1.0 mg SEMA (mean baseline was 76.4 kg)[17]	
	SEMA 1.0 mg (n = 404) or EXE ER 2.0 mg (n = 405) (56-week follow-up) (SUSTAIN 3)[18]	Patients with T2 DM, taking oral antidiabetic agents (n = 813)[18]	HbA_{1c} decreased by 1.5% with SEMA; decreased by 0.9% with EXE (from baseline 8.3%) BW decreased by 5.6 kg with SEMA; decreased by 1.9 kg with EXE (mean baseline was 95.8 kg)[18]	
	SEMA 0.5 mg (n = 362) SEMA 1.0 mg (n = 360) Glargine (n = 360) (30 wk follow-up) (SUSTAIN-4)[19]	Patients with T2 DM, with insufficient glycemic control with metformin either alone or in combination with a sulfonylurea (n = 1,089)[19]	HbA_{1c} decreased by 1.21% with 0.5 mg SEMA; decreased by 1.64% with 1.0 mg SEMA; decreased by 0.83% by glargine (from baseline 8.17%) BW decreased by 3.47 kg with 0.5 mg SEMA; decreased by 5.17 kg with 1.0 mg SEMA; and increased by 1.15 kg by glargine (mean baseline was 93.45 kg)[19]	
	SEMA 0.5 mg (n = 132) SEMA 1.0 mg (n = 131) Placebo (n = 133) (30-30 week follow-up) (SUSTAIN-5) [20]	Patients with T2DM uncontrolled with basal insulin with or without metformin (n = 397)[20]	HbA_{1c} decreased by 1.4% with 0.5 mg SEMA; decreased by 1.8% with 1.0 mg SEMA; and decreased by 0.1% by placebo (from baseline 8.4%) BW decreased by 3.7 kg with 0.5 mg SEMA; decreased by 6.4 kg with 1.0 mg SEMA; and decreased by 0.4 kg with placebo (mean baseline was 91.7 kg)[20]	
	SEMA 0.5 mg (n = 826) SEMA 1.0 mg (n = 822) Placebo (n = 1,649) (104-week treatment period with a 5-week follow-up period) (SUSTAIN-6)[21]	Patients with T2DM on a standard-care regimen (n = 3,297)[21]	HbA_{1c} decreased by 1.1% with 0.5 mg SEMA; decreased by 1.4% with 1.0 mg SEMA; and decreased by 0.4% by placebo (from baseline %8.4) BW decreased by 3.6 kg with 0.5 mg SEMA; decreased by 4.9 kg with 1.0 mg SEMA; and decreased by 0.7 kg by placebo (mean baseline was 91.7 kg)[21]	
HT	EXE 5 µg twice daily, LIRA, 1.2 mg/day EXE 2 mg/week once weekly (at least 20-20 week follow-up)[30]	Participants with a BMI of 25 or higher; with or without T2DM[30]	Increasing in BP in short term Decreasing BP in long-term LIRA (2–7 mm Hg from baseline), EXE (2–3 mm Hg from baseline)	Increasing HR and cardiac output Decreasing proximal tubular sodium resorption, leading to lower GFR dilating of afferent arteriole
	LIRA 1.2 (n = 228) LIRA 1.8 (n = 234) ROSI (n = 232) Placebo (n = 114) (26-week follow-up) (LEAD-1)[33]	Patients with T2DM (n = 1,041)[33]	LIRA (1.2–2.6 mm Hg from baseline) LIRA (1.8–2.8 mm Hg from baseline) ROSI (–0.9 mm Hg)	
	LIRA 0.6 (n = 100) LIRA 1.2 (n = 100) LIRA 1.8 (n = 100) Placebo (n = 100) Glımeprid (n = 100) (26-week follow-up) (LEAD-II)[34]	Patients with T2DM (n = 1,091)[35]	LIRA 1.2 (–2.8 mm Hg) LIRA 1.8 (–2.3 mm Hg) Glimepiride (+0.4 mm Hg)	

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Table 1 (continued)

	Agent	Subjects	Effect	Mechanism
	LIRA 1.8 (n = 230) Glargine (n = 232) Placebo (n = 114) (26-week follow-up) (LEAD-V)[35]	Patients with T2DM (n = 581)[35]	LIRA −4.0 mm Hg versus Glargine +0.5 mm Hg	
Non-alcoholic fatty liver disease	LIRA 1.8 mg/d (n = 26) or placebo (n = 26) (48 week follow-up)[56]	Patients with NASH (n = 52)[56]	Resolution of NASH Decreasing progression to fibrosis	Anti-inflammatory mechanisms improving weight, IR, and glycemic control
	SEMA 0.1 mg/d (n = 80), 0.2 mg/d (n = 78), 0.4 mg/d (n = 82), placebo (n = 80) (72 week follow-up)[57]	Patients with NASH (n = 320)[57]	Resolution of NASH Decreasing worsening of fibrosis	
Cardiovascular Disease	ALBI 30–50 mg (n = 4,731) Placebo (n = 4,732) (1.5-years follow-up) (HARMONY) [64]	Patients with DM and CVS disease (n = 4,963)[64]	Improving major adverse cardiovascular events (first nonfatal acute myocardial infarction, nonfatal stroke, or cardiovascular death)	Effects on endothelial function, intima media thickness atherosclerosis, plaque stability Improving cardiac blood supply, cardiac output, ventricular contractility, myocardial glucose uptake, ischemia tolerance, left ventricular ejection fraction, cardiac index, pulmonary capillary wedge pressure Reducing cardiac fibrosis reductions in BW and cardiometabolic risk factors, including WC, systolic and diastolic BP, fasting lipid levels, and inflammatory markers
	DULA 1.5 mg (n = 4,949) Placebo (n = 4,952) (5.4 years of follow-up) (REWIND)[65]	Patients with DM who had either a previous CVS event or CVS risk factors (n = 9,901) [65]		
	LIRA 1.8 mg (n = 4,668) Placebo (n = 4,672) (3.8-years follow-up) (LEADER)[66] SEMA 0.5 mg (n = 826)	Patients with DM and high CVS risk (n = 9,340) [66]		
	SEMA 1.0 mg (n = 822) Placebo (n = 1,649) (104-week treatment period with a 5-week follow-up period) SUSTAIN-6) [21]	Patients with T2 DM (n = 3,297), on a standard-care regimen[21]		
Polycystic ovary syndrome (PCOS)	MET 1000 mg BID arm (n = 14), LIRA 1.2 mg arm (n = 11), combination arm (n = 11) (12-week follow-up)[83]	Women with obesity and PCOS under MET therapy at least 6 months (n = 40)[83]	Significant weight loss Decreasing WC Reducing glucose and androstenedione levels	Reducing BW Reducing visceral fat adiposity Increasing insulin sensitivity
	LIRA 1.8 mg (27.8-7.8 weeks follow-up)[84]	Women with PCOS, who have overweight or obesity (n = 84)[84]		
	LIRA 1.2 mg alone (n = 21), MET 1000 mg BID + LIRA 1.2 mg combination arm (n = 22), (12-week follow-up)[87]	Women with obesity and PCOS (n = 43)[87]		
The reproductive system	MET 1000 mg BID arm (n = 14), MET 1000 mg BID + LIRA 1.2 mg combination arm (n = 13) for 12 weeks, 12-month pregnancy rate follow-up[96]	Infertile women with obesity and PCOS (n = 28)[96]	Increasing pregnancy rates, per embryo transfer, and cumulative pregnancy rates	Reducing BW Decreasing aromatization of the androgens in adipose tissue Increasing GnRH pulsatile release
	Placebo (n = 24), LIRA 1.8 mg (n = 48), (26-week follow-up)[89]	Women with overweight or obesity and PCOS[89]	Amelioration ovarian dysfunction Improving bleeding regularity Reducing free testosterone levels	Reducing BW Reducing IR Increasing SHBG levels
	LIRA 3 mg alone (n = 15), 50 mg 1% transdermal testosterone gel alone (n = 15), (16-week follow-up)[98]	Men with obesity (n = 30)[98]	Increasing total testosterone levels Rise in SHBG level Significant recovery of HPT axis Significant improvement of sexual symptoms	Reducing BW Decreasing aromatization of androgen to estrogen Increasing pulsatile GnRH release
	MET 2000–3,000 mg/d for 1 year+1,000 mg testosterone undecanoate 1,000 mg/d every 12 weeks. LIRA 1.2 mg was added to poor responders for a second year. Therapy continued for another year in the good responders[28]	43 Patients with T2DM and obesity, with overt hypogonadism and erectile dysfunction[28]	Achieving normal serum testosterone levels Improving erectile dysfunction	Reducing BW Improvement in other metabolic parameters (glucose, BP, and lipids)

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Table 1 (continued)

	Agent	Subjects	Effect	Mechanism
Obstructive sleep apnea	LIRA 3.0 mg (n = 180) or placebo (n = 179) (32-week of follow-up)[105]	PwO with moderate or severe OSA[105]	Improvement in OSA symptoms greater reductions in apnea-hypopnea index, number of apnea events per hour and improved oxygen saturation, sleep architecture, and sleep/health-related quality of life endpoints	Reducing BW
Osteoarthritis	LIRA (3 mg/day) LIRA 3 mg (n = 80) Placebo (n = 76) (52 weeks of follow-up)[110]	People with overweight, obesity, and osteoarthritis (n = 156)[110]	Significant weight loss at >52 weeks but did not reduce knee pain	-Reducing BW
Central nervous system disorders	LIRA (1.8 mg daily after titration for 3 weeks) (Mean time to loss in each group around 4 months)[124]	MET-treated PwO (n = 16) either diagnosed with T2DM or prediabetes compared to lifestyle changes (n = 16) arm[124]	Significant improvement in short term and composite memory scores in PwO compared to lifestyle changes arm in the trial	The effect was significant even though groups had equal weight loss
	LIRA (0.6 mg initiation and 1.8 mg maximum dose) T2 DM (n = 24, controls (n = 23) (12-week follow-up) [125]	Patients with obesity and T2 DM[125]	LIRA group had better performance compared to controls in total learning, MMSE and naming scores Increased brain activation in the DLPFC and in the OFC	BMI and fasting blood glucose levels did not predict the changes observed; however, LIRA significantly increased DLPFC and orbitofrontal cortex activation, which correlated with MMSE improvement
	LIRA 1.8 mg (n = 18) or placebo (n = 20) (26-week trial)[126]	Patients with Alzheimer's disease Patients with diabetes were excluded[126]	Overall, a cerebral metabolic rate decline observed in placebo groups was not observed in the LIRA group; however, cognitive scores evaluated with the brief cognitive examination of Wechsler Memory Scale were not different in or between the groups at 6 months, while the LIRA group had a longer duration of Alzheimer's onset. Session 2/session 1 ratios of CMRglc in the cingulate and occipital lobes declined significantly compared to the LIRA group	Even though the change in weight, BMI, and systolic BP improved in the LIRA group compared to placebo, authors did not report how it affected the cognitive measurements
	EXE 2 mg EXE 2 mg (n = 31), Placebo (n = 29) (48 48 weeks of treatment and 12 weeks' washout)[127]	Patients with Parkinson's disease[127]	Though groups were not different for on medication scores of UPDRS part 3 scores (motor symptoms), at 60 months, placebo groups showed a 2.1 point worsening, whereas the EXE group showed 1 point improvement (p = 0.0318)	Compared to placebo, the reduced rate of dopamine transporter binding was found in right and left putamen and right caudate in the EXE group. Weight loss did not affect the change in the primary outcome
	EXE 10 µg twice daily (n = 23) (at least 3- mts follow-up)[128]	Patients with obesity and T2DM[128]	Compared to patient on not on GLP-1 agonists, patients on EXE reported higher depressive scores as assessed with PHQ-9 (9.70±4.92 vs. 6.70±4.66, p = 0.026) and cognitive failures as assessed with CFQ (29.52±12.06 vs.); however, this finding could be due to increased perceived stress	EXE use effect on high depressive scores was not direct, but through higher perceived stress levels
Cancer	LIRA[136, 137]	Human pancreatic cells	Inhibiting growth Promoting apoptosis Enhancing the chemosensitivity	cAMP-dependent manner, inhibiting PI3K/AKT signaling pathway
	LIRA[138]	MCF-7 human breast cancer cells	Limiting the viability of MCF-7 human breast cancer cells	Modulating the adipocytokines and their receptors
	LIRA[141]	Hepatocellular carcinoma cells	Inducing autophagy and senescence	Through the increase of TGF-β1
	EXE and LIRA[139,140]	Endometrial carcinoma cells	Inhibiting the proliferation of tumor cells	Through the AMPK signaling pathway
	EXE and LIRA[142]	Prostate cancer cells	Attenuating prostate cancer growth	Regulating P38 pathway

LIRA, liraglutide; T2DM, type 2 diabetes mellitus; BW, body weight; BMI, body mass index; SEMA, semaglutide; GLP, glucagon-like peptide; HT, hypertension; HR, heart rate; GFR, glomerular filtration rate; NASH, nonalcoholic steatohepatitis; WC, waist circumference; PwO, people with obesity; EXE, exenatide; MMSE, Mini-Mental State Examination; DLPFC, dorsolateral prefrontal cortex; MFC-7, Michigan Cell Foundation breast cancer cell line; cAMP, cyclic AMP; PI3K/AKT, phosphatidylinositol-3-kinase/Akt; TGF-β1, transforming growth factor-beta 1.

glutamatergic transmission in the brain, GLP-1 RAs may decrease palatable food and substance consumption [122]. However, a cross-sectional study reported no direct effect of EXE use on depressive scores compared to the group of diabetic patients with obesity not on GLP-RAs [129].

Drug Effect

Current studies report that the effect of GLP-1 modification on cognitive changes may be independent of the change in weight [121, 122, 124]. Effects of GLP-1 RAs for central nervous system manifestations related to obesity are mainly protection against cognitive impairment and changing the reward responses, but more data on humans and neuropsychiatric disorders are needed on this topic.

Cancer

A strong association between obesity and incidence of several cancers, including endometrium, breast, pancreas, hepatocellular, kidney, colon, rectum, and esophagus cancers, is observed in epidemiological studies [130]. Higher BMI was also reported to increase the risk of prostate and bladder cancer [131, 132]. IR and chronic hyperinsulinemia, high IGF levels, and increased bioavailability of steroid hormones, adipose tissue-derived hormones, and proinflammatory cytokines might be related to obesity-associated tumorigenesis [133].

GLP-1 RAs have been associated with both increased cancer risk and inhibition of tumor growth and metastases. Especially, the results of preclinical and epidemiological studies regarding the risk for pancreas and thyroid cancers are conflicting [134]. No clear clinical evidence has been found to conclude the tumorigenic effect of GLP-1RAs to date.

Some preclinical studies suggested a potentially beneficial effect on the development of some types of cancers with GLP-1 RA treatment. It was shown that GLP-1 or GLP-1 RAs can inhibit a variety of tumor cells [135–137].

Drug Effect

Activation of GLP-1 R by LIRA inhibits growth and promotes apoptosis of human pancreatic cancer cells in a cAMP-dependent manner, inhibits PI3K/AKT signaling pathway [137], and enhances the chemosensitivity of pancreatic cancer cell [138]. GLP-1 inhibits breast cancer cell proliferation, through cAMP induction [136]. Treatment with LIRA reduced the levels and expression of leptin and its receptors, while increasing the expression of adiponectin and its receptors in both obese adipose tissue-derived stem cells and MCF-7 human breast cancer cells incubated in obese adipose-derived stem cells-conditioned medium. LIRA seems to limit the viability of MCF-7 cells via modulating the adipocytokines and hence block their impact on tumor growth [139]. EXE and LIRA both inhibited the proliferation of endometrial carcinoma cells, through the AMPK signaling pathway [140, 141]. The antiproliferative activity of EXE and LIRA has been reported on human prostate and hepatocellular carcinoma cells [142, 143]. Thus, there is abundancy of preclinical data about the antitumorigenic effect of GLP-1 RAs. More clinical data are anticipated in this area in the near future. Summary of the effects and mechanisms of GLP-R analogs on complications of obesity are shown in Table 1.

Conclusion

In conclusion, GLPR-1 RAs seem to be effective on complications of obesity, proven through preclinical and clinical studies. The effects are not only through improvements in BW and glycemic control but also on IR, anti-inflammatory, antioxidative, antifibrotic, and hemodynamic processes. Further data are needed in terms of observing the influences in long-term randomized studies with different doses of different GLP-1 RAs approved for obesity. Moreover, both preclinical and clinical data are needed to enlighten the mechanisms of their effects.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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