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Pharmacologic Management of Obesity after Liver Transplantation: A Critical Review

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Abstract

Post liver transplant obesity is associated with the development of metabolic disorders such as diabetes mellitus and nonalcoholic fatty liver disease and is a strong predictor of post-transplant mortality. Anti-obesity pharmacotherapy could serve as an effective adjunct to lifestyle modification in the post-transplant setting. Currently, utilization of anti-obesity medication in post liver transplant patients is limited by scarce data on their efficacy and safety in the post-transplant setting. Newer classes of anti-obesity medications, including the glucagon-like peptide 1 agonists (GLP-1) do not only help with weight loss but are effective anti-diabetic agents and are in further development for their potential hepatoprotective and renoprotective effects and reduction in cardiovascular risk. The objective of this manuscript was to critically review the efficacy and safety of anti-obesity pharmacotherapy in post-liver transplant patients.

Keywords

Obesity; Weight loss; GLP-1 agonists; Liver transplant; Solid organ transplant; Anti-obesity medication

Introduction

Post transplant obesity is associated with increased risk of several metabolic complications including diabetes mellitus (DM), non-alcoholic fatty liver disease (NAFLD), and cardiovascular disease and is a strong predictor of post-liver transplant mortality [1–3]. With the rise in obesity pandemic, it is expected that the prevalence of obesity and weight-related comorbidities will increase in pre- as well as post-liver transplant patients. Patients with severe obesity are at an increased risk of death on the liver transplant waitlist [4] due to a number of factors including higher risk for clinical decompensation and worsening portal hypertension [5–7], decreased odds of receiving model of end stage liver disease (MELD) exception points, and increased risk of being turned down for an organ [8,9]. Strategies for

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weight loss should be explored and implemented ideally prior to liver transplant, however sicker patients with high MELD scores may not have adequate time to achieve weight loss prior to transplant. Approximately 46% of patients receiving liver transplant developed metabolic syndrome [10–12], with pretransplant obesity being a major risk factor for post-transplant obesity [13,14]. Post-transplant obesity is associated with the development of a variety of metabolic disorders and increased mortality [1–3].

Obesity is closely associated with NAFLD, DM, cardiovascular disease, among other chronic health conditions. The aggressive subtype of NAFLD, nonalcoholic steatohepatitis (NASH) is currently the second leading cause of liver transplantation in the United States [15]. After liver transplantation, the risk of graft steatosis is highly increased in patients with previous history of NASH typically due to persisting risk factors [16]. Moreover, the presence of DM which increases cardiovascular disease risk severely affects the prognosis of liver transplant patients [17,18]. Exercise and a low-calorie diet in live liver donors leads to improved graft outcome in recipients [19].

While the cornerstone of obesity treatment remains lifestyle modification including hypocaloric diet and increased physical activity, the reality is that these strategies are unfortunately unattainable or inadequate in producing significant and sustainable weight loss in majority of patients. Anti-obesity medications and bariatric surgical interventions could serve as effective adjuncts to weight loss even in the post liver transplant setting. There is data supporting bariatric surgery particularly sleeve gastrectomy in carefully selected patients with obesity after transplant [20–23]. Although bariatric surgery is the most effective anti-obesity management strategy conferring average weight loss of 30–40% from baseline, the risk of surgical complications and its irreversible nature may deter potential candidates. Moreover, the degree of excess weight may not reach the threshold for consideration for bariatric surgery based on current guidelines.

Historically, anti-obesity medications conferred about 5% weight loss versus the substantially higher weight loss potential of bariatric surgery. This led to the so called “treatment gap” which denoted the lack of therapeutic strategies to confer ≥ 10 to ≥ 15% weight loss that frequently leads to substantial improvement in overall health and weight related comorbidities. The emergence of new and effective anti-obesity pharmacotherapy over the past decade that results in ≥ 10% weight loss has revolutionized the treatment of overweight and obesity. The newer glucagon like peptide-1 agonists (GLP-1As) have filled the treatment gap; and combination of GLP-1As and other incretins such as gastric intestinal peptide (GIP) also appear promising in producing substantial weight loss through non-surgical means.

Given the rise in obesity and weight-related complications, which is reflected in the changing demographics of liver transplant candidates with NASH surpassing chronic hepatitis C as indication for liver transplant, it is even more crucial that strategies for weight management are implemented not only prior to transplant but also in the post-transplant setting. There are currently no prospective studies on anti-obesity pharmacotherapy in the post-liver transplant setting. Here, we review the available data on use of anti-obesity medications in post-liver transplant patients, with majority of the studies analyzing

retrospective data in patients treated with GLP-1 agonists prescribed primarily for management of diabetes mellitus.

Overview of Anti-obesity Pharmacotherapy

The cornerstone of initial management of overweight and obesity necessitates sustainable behavioral, nutritional and physical activity modifications that confer a negative caloric balance. These methods however, are typically insufficient for achieving significant and long-term weight loss; one-third to two-thirds of patients regain weight within one-year following the end of lifestyle intervention, and almost all patients regain weight within 5 years [24]. Anti-obesity medications should be recommended for individuals with obesity with BMI ≥ 30 kg/m^2 or overweight with BMI ≥ 27 kg/m^2 with weight-related comorbidities who are unable to achieve clinically significant weight loss, defined as ≥ 5% of baseline weight [25] after 6 months of lifestyle interventions. Principles of anti-obesity pharmacotherapy include understanding that it is a lifelong treatment because obesity is a chronic disease; discontinuation of anti-obesity medication(s) after initial weight loss generally leads to weight regain. Moreover, there is significant inter-individual variability in response to anti-obesity medications [26]. Choosing an appropriate anti-obesity medication depends on the patient's comorbidities, potential drug-drug interactions, allergies and side effects. Initiation of any anti-obesity medication requires following for efficacy, safety, and tolerability. The FDA-approved anti-obesity medications currently on the market are: phentermine, orlistat, phentermine/topiramate extended release, naltrexone sustained release (SR)/bupropion SR, liraglutide, and semaglutide. Other medications used off-label for obesity treatment include metformin, buproprion, topiramate, several GLP-1 agonists including dulaglutide, exenatide, and dual GLP-1 agonist/gastric inhibitory polypeptide (GIP) agonist tirzepatide.

Efficacy of Anti-obesity Pharmacotherapy in Patients with Versus without Diabetes Mellitus

Patients with obesity and co-existing DM typically experience less weight loss with anti-obesity pharmacotherapy compared to those without DM. When treated with GLP-1A versus placebo, individuals with obesity and DM demonstrate a mean weight loss difference of 4–6.2%, while those with obesity but without DM show a higher mean weight loss difference of 6.1-17.4% [27]. A variety of reasons for the observed difference in therapeutic response to anti-obesity pharmacotherapy between diabetic versus non-diabetic individuals have been proposed, including the higher likelihood of being on weight gain-promoting medications in patients with DM; fear of hypoglycemia in patients with DM which may result in compensatory behaviors that ultimately hamper weight loss efforts; altered microbiota among patients with DM; decrease in glycosuria resulting in less weight loss in those with DM, among others [27]. This known discrepancy in pharmacotherapy-induced weight loss among patients with versus without diabetes is important for the reader in assessing the studies below that were conducted primarily among patients with DM.

Retrospective Studies of Anti-obesity Pharmacotherapy in Post-transplant Liver Patients

Lipase inhibitor Orlistat

Orlistat (trade name Xenical) is a gastric lipase and pancreatic lipase inhibitor that promotes weight loss by decreasing fat absorption from the gastrointestinal tract. Orlistat achieves weight loss of about 3-5% from baseline. The most common side effects are steatorrhea due to impaired fat absorption that could potentially result in deficiency of fat-soluble vitamins and nutrients [28].

In a prospective, open label trial to study the safety of orlistat in 15 patients with obesity and overweight following liver transplant on a stable tacrolimus-based immunosuppressive regimen, no intolerance, adverse effect or rejection was noted during the course of the study [29] (Table 1). Patients were on orlistat 120 mg three times daily for 6 months or 120mg daily for 3 months. Tacrolimus dose reduction was necessary in 4 patients, and dose increase in 2 patients out of the 12 patients who completed the study. A significant decrease in waist circumference was noted at the end of treatment period compared to baseline, however body weight and BMI were unchanged. Thus, Orlistat treatment appeared to be well- tolerated and safe post liver transplant, as long as attention is paid to immunosuppressive drug levels and dietary adherence [29].

Glucagon-Like Peptide-1 Receptor Agonists

Glucagon-like peptide-1 agonists (GLP-1As), also known as Glucagon-like peptide-1 receptor agonists (GLP-1-RAs) or incretin mimetics slow gastric emptying and promote satiety. GLP-1As were initially approved for treatment of DM; subsequently two GLP-1As have been approved for treating obesity as well, although most GLP-1As are used off-label as obesity pharmacotherapy especially when other weight-related comorbidities are present. The first GLP-1A, exenatide, was approved by the US Food and Drug Administration (FDA) in April 2005 for treatment of DM. In 2014, the FDA approved liraglutide as the first GLP-1A for weight management. Liraglutide is administered once daily up to a maximum dose of 3.0mg. In 2021, the next generation GLP-1A semaglutide was approved, dosed once weekly up to 2.4 mg. Structural changes in semaglutide, as compared to liraglutide, confer greater efficacy for weight loss and allow for weekly dosing compared to the daily dosing of liraglutide [30]. Side effects of GLP-1As, typically gastrointestinal, can be managed by switching class and personalizing the dose adjustment regimen [31].

Below, we review four retrospective studies of GLP-1As in patients with liver transplant and other solid organ transplants. Due to our primary focus on liver transplant patients, all the publications reviewed contained individuals with history of liver transplant (with or without other organ transplants).

Dulaglutide

Singh, et al. [32] performed a retrospective study assessing the efficacy of dulaglutide in 63 patients with DM and solid organ transplants (kidney, n = 51; liver, n = 10; liver/kidney, n = 1; heart n = 1). Dulaglutide starting dose was 0.75 mg once weekly to a maximum of 1.5

mg weekly. When comparing the mean weight change after a follow-up period of 6, 12, and 24 months, weight loss of 2.07kg, 4kg, and 5.23kg respectively was noted, corresponding to a reduction in the mean BMI by 0.80, 1.35, and 2.01. A mean paired difference for decreased insulin requirement by 5.94 units was seen before versus after treatment with dulaglutide. Non-severe hypoglycemic events not requiring hospitalization were noted in 4 patients. Gastrointestinal side effects were noted in 1.5% to 3% of patients, and no dose adjustments of immunosuppressive medications were necessary [32].

Dulaglutide/Liraglutide

Singh, et al. [33] also performed a retrospective study comparing the safety and efficacy of dulaglutide and liraglutide in 88 patients with DM and solid organ transplant. The dulaglutide group (kidney, n = 51; liver, n = 10; liver/kidney, n = 1; heart n = 1) was started on a dose of 0.75 mg once weekly which was increased to 1.5 mg once weekly. Weight loss among those on dulaglutide by 2%, 4%, and 5.2% at 6, 12, and 24 months, respectively, compared to baseline was noted, with accompanying decrease in the median HbA1C by 10%, 5.3% and 8.4%, respectively, during those time periods [33]. A reduction in insulin requirement by 26% was noted at 24 months. The liraglutide group (kidney, n = 21; liver, n = 1; liver/kidney, n = 2; heart, n =1) were started at 0.6 mg daily and increased to 1.2 mg daily. Weight loss by 0.09%, 0.87%, and 0.89% at 6, 12, and 24 months compared to baseline was noted, with accompanying decrease in median hemoglobin A1C by 5.3%, 3%, and 2%, respectively, compared to baseline. Insulin requirement decreased by 3.6% at 24 months. Side effects reported were mainly nausea, vomiting, and diarrhea. A non-significant dose adjustment of immunosuppression medications was reported in both dulaglutide and liraglutide groups [33]. At 24 months, the dulaglutide group demonstrated reduction in creatinine level by 10% with a 15% increase in estimated glomerular filtration rate (eGFR), while the liraglutide group demonstrated an increase in creatinine by 7% with an 8% decrease in eGFR. The study suggested that compared to liraglutide, dulaglutide showed superior efficacy and safety profiles in post solid organ transplant patients. The longer duration of action of the weekly dose dulaglutide compared to the daily dosed liraglutide may partly account for this superior efficacy [33]. It is unclear if the different dosing frequencies affected medication compliance.

Dulaglutide/ Exanetide/ Liraglutide/ Semaglutide

Thangavelu, et al. [34] conducted a retrospective analysis assessing the safety and efficacy of dulaglutide, exanetide, liraglutide or semaglutide in post-transplant patients (liver, n = 7; heart, n = 5; and kidney, n = 7) with either pre- or post-transplant diagnosis of DM. A statistically significant decrease in body weight by a mean of 4.86 kg from baseline was seen after 12 months. Also, hemoglobin A1C decreased by 0.75 % from baseline , and insulin requirement decreased by 16.25 units at 12 months post-transplant. Side effect of nausea was noted in 5 patients. No significant changes in tacrolimus levels and renal function were noted during the study period [34].

Sweiss, et al. [35] conducted another retrospective study assessing the safety and efficacy of dulaglutide, exenatide, liraglutide and semaglutide in 118 patients post solid organ transplant (liver, n = 23; kidney, n = 82; “liver/kidney”, n = 3; lung, n = 8; kidney/pancreas, n = 1).

In this study, nadir values assessed 3 to 12 months after initiation of GLP-1A were used. A statistically significant decrease in mean body weight by 2% and mean BMI by 5% were noted between baseline measures and nadir values. Also, median hemoglobin A1C level decreased from 8% to 7%, and median fasting glucose level decreased from 139 to 115 units. Of note, majority of the patients were started on other anti-diabetic medications during the study period, including metformin, dipeptidyl peptidase 4 (DPP4) inhibitors, among others which may have impacted the weight loss observed as well as the improvement in diabetic control that was noted. Similar to other studies, gastrointestinal side effects such nausea and vomiting were the most common side effects, and two patients discontinued the medication due to adverse events [35].

Other Anti-obesity Pharmacotherapies

To date, the most commonly used anti-obesity medication in the non-transplant setting is phentermine (Lomaira; Adipex P), a sympathomimetic drug that stimulates hypothalamic adrenergic neurotransmitters, increases energy levels, and reduces appetite. One clinical trial showed a 19% decrease in hepatic steatosis in bariatric surgery candidates on phentermine [36; there are no studies of phentremine use in liver transplant patients. Phentermine/ topiramate combination (Qsymia) confers a higher degree of weight loss than phentermine alone, with weight loss up to 10% from baseline in non-transplant settings [37]. The combination demonstrates weight loss superiority over liraglutide as well [38]. The combination of naltrexone/bupropion (Contrave) results in weight loss of about 6% in non-transplant settings [39]. Recently, tirzepatide, a dual GLP-1A and GIP agonist administered weekly, demonstrated a mean percent weight change of 15% across three different doses in a 72-week clinical trial of non-transplant patients with overweight or obesity [40]. The highest dose of 15mg resulted in 20.9% weight loss compared to 3.1% for placebo. The FDA granted a Fast Track designation in October 2022 to develop tirzepatide as an anti-obesity medication.

Conclusions

Obesity is associated with the development of several cardiometabolic conditions and is a strong predictor of mortality in patients post liver transplant. As lifestyle modification geared at hypocaloric diet and increased physical activity is often inadequate in producing significant and sustainable weight loss, anti-obesity pharmacotherapy can serve as an effective adjunct. In a small open label study of orlistat in 15 patients post liver transplant, a significant decrease in waist circumference was noted but with no change in body weight and BMI [29]. Retrospective studies of GLP-1As suggest that these agents are safe and efficacious in producing weight loss in the post-liver transplant setting as well as in those with other solid organ transplants (Figure 1). Limitations of the currently available literature on the topic include their retrospective nature and small sample sizes. In addition, patients in these studies had co-existing DM, potentially limiting the observed weight loss given the known lower efficacy of anti-obesity pharmacotherapy in patients with DM.

Our review highlights the significant differences in weight loss among post-transplant patients not only from individual variability but also from differences in pharmacotherapy.

Also, adverse events among post-transplant patients on anti-obesity agents were similar to that seen in the non-transplant population. Moreover, immunosuppression doses in post-transplant patients are typically not affected by treatment with GLP1-As. Furthermore, GLP-1A use is associated with improvement in cardiometabolic status. In summary, our review provides critical insight on the use of anti-obesity medications in post liver transplant patients, informing the future applicability of these agents for improving post-transplant outcomes.

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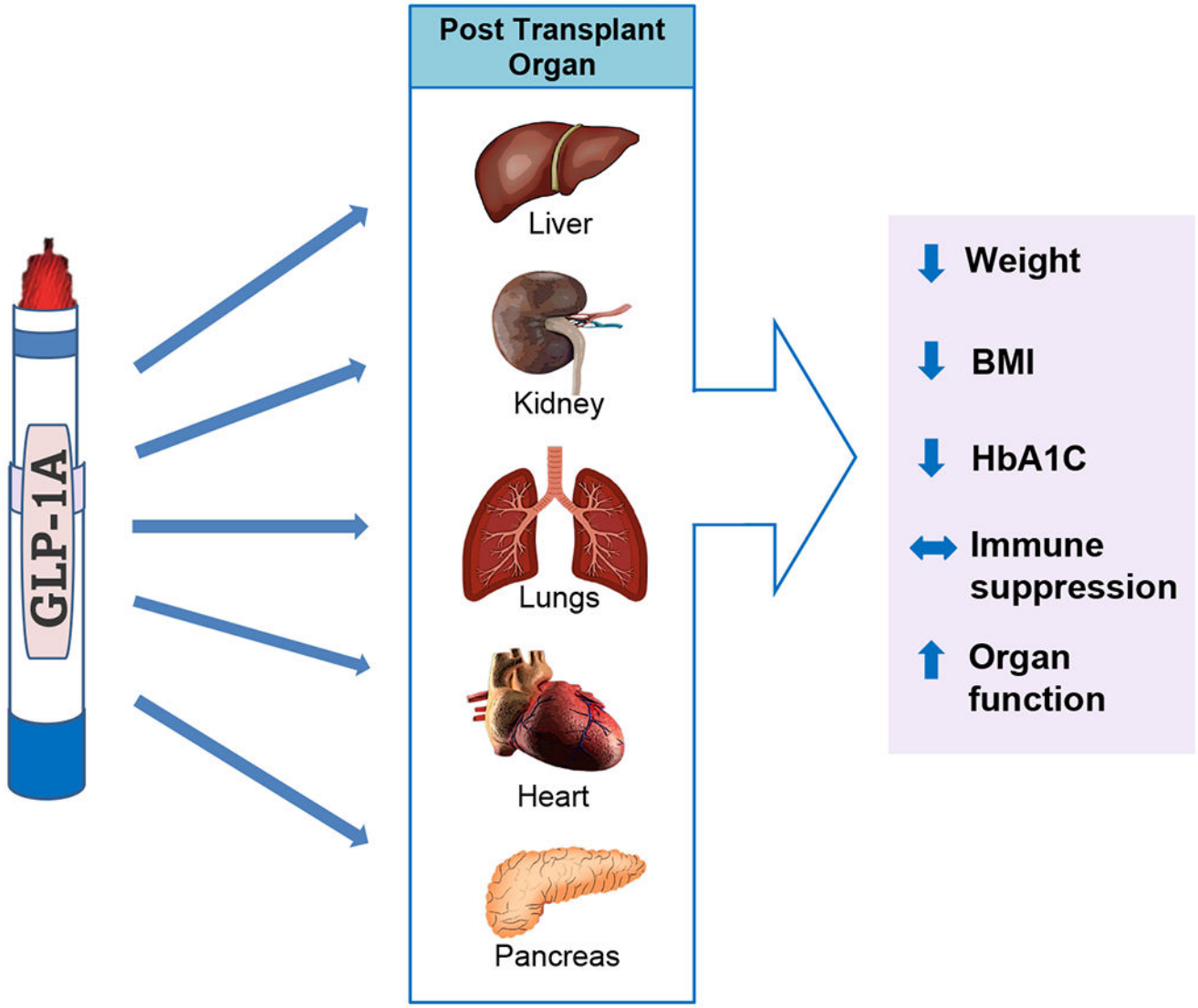

Figure 1:

Glucagon like peptide 1 agonists (GLP-1A), also called glucagon like receptor agonists or incretin mimetics currently have the most data in the context of weight management post liver transplant and other solid organ transplants. GLP-1A treatment is associated with significant weight loss and improved glycemic control without the need for immunosuppression dose adjustment. GLP-1A treatment is also associated with improvement in cardiometabolic status and organ-specific function.

Table 1:

Anti-obesity pharmacotherapy in patients with liver transplant and other solid organ transplants.

Author	Medication used	Sample size and organ transplanted	Goal	Efficacy relating to weight loss	Other outcomes	Side effects/ complication
Cassiman,et al. [29]	Lipase inhibitor: Orlistat	15 patients Liver (15)	Evaluate safety of orlistat in the management of overweight and obesity in liver transplant recipients on tacrolimus-based immunosuppressive regimens.	Weight loss was observed but did not reach statistical significance.	Non-significant decrease in BMI. Significant decrease in waist circumference from 109.7 +/− 11.9 cm at baseline to 97.3 +/− 11.2 cm at 6 months; 97.7 +/− 9.1 cm at 9 months; 97.7 +/− 9.4 cm at 12 months; (p <0.01 versus).	No side effects, suggesting strict adherence to the prescribed dietary fat restrictions.
Singh, et al. [32]	GLP-1A: Dulaglutide	63 patients Liver (10) Kidney (51) Kidney/liver (1) Heart (1)	Management of DM in solid organ recipients.	Mean paired difference for weight reduction: 2.07 kg (p<0.003) at 6 months; 4.07 kg (p<0.001) at 12 months; 5.23kg (p<0.034) at 24 months.	Mean paired difference for BMI reduction: 0.80 kg/m^2 (p<0.001) at 6 months; 1.35 kg/m^2 (p <0.005) at 12 months; 2.015 kg/m^2 (p<0.045) at 24 months.	Nausea, vomiting, diarrhea, or abdominal pains were experienced by 1.5-3% of patients.
Singh, et al. [33]	GLP-1A: Dulaglutide Liraglutide	88 patients Liver (11) Kidney (72) Liver/kidney (3) Heart (2)	Compare safety and efficacy of dulaglutide versus liraglutide in terms in solid organ transplant recipients.	Weight loss percent compared to baseline for Dulaglutide vs Liraglutide: 2% vs 0.09% (p=0.003) at 6 months; 4% vs 0.87% (p=0.005) at 12 months; 5.2 % vs 0.89% (p=0.05) at 24 months.	Decrease in BMI for Dulaglutide vs Liraglutide: 2.4% vs 0.24% (p=0.01) at 6 months; 6% vs 1.4% (p=0.009) at 12 months; 8% vs 0.54% (p=0.04) at 24 months. Decreased insulin requirement for Dulaglutide vs Liraglutide: 26% vs 3.6% (p=0.01).	Lower rate of gastrointestinal side effects for Dulaglutide vs Liraglutide, including nausea (3% vs 8%); vomiting (1.5% vs 4%); diarrhea (3% vs 12%); abdominal pain (0% vs 4%). Cholelithiasis was reported only with Liraglutide (4%).
Thangavelu, et al. [34]	GLP-1A: Exanatide Liraglutide Dulaglutide Semaglutide	19 patients Liver (7) Kidney (7) Heart (5)	Evaluate efficacy and safety of GLP-1A in the management of DM in solid organ transplant patients.	Mean weight loss compared to baseline: 2.42 kg (95% CI −3.88, −0.96) at 3 months; 2.84 kg (95% CI −4.94, −0.74) at 6 months; 4.86 kgs (95% CI −7.79, −1.93) at 12 months.	No change in immunosuppression. No change in transplant outcomes. Statistically significant decrease in BMI from baseline: −0.89 (95% CI −1.44, −0.33) at 3 months; −1.07 (95% CI −1.8, −0.29) at 6 months and −1.63 (95% CI −2.53, −0.73) at 12 months	Nausea was reported by 5 patients; 3 patients stopped taking the medication due to gastrointestinal side effects.
Sweiss, et al. [35]	GLP-1A: Dulaglutide Exenatide Liraglutide Semaglutide	118 patients Liver (23) Kidney (83) Lung (8) Kidney/Liver (3) Kidney/ Pancreas (1)	Evaluate safety and efficacy of GLP-1A in the management of DM in post-transplant patients.	Median weight loss 0.2 kg (p<0.0001) was observed in the study population compared to baseline.	Statistically significant decrease in fasting blood glucose from 139 to 115 mg/dL (p<0.0001); HbA1c from 8 to 7% (p<0.001); BMI from 32 to 31kg/m^2 (p=0.0008); serum creatinine from	9 patients reported at least one hypoglycemic episode, 5 patients developed pancreatitis. Gastrointestinal

Author	Medication used	Sample size and organ transplanted	Goal	Efficacy relating to weight loss	Other outcomes	Side effects/ complication
					1.2 to 1.08 mg/dL ($p<0.0001$); eGFR increase from 55 to 61 mL/min ($p<0.0001$).	side effects (nausea, vomiting and diarrhea) were reported in 16 patients.