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Review Article

Underuse Of GLP-1 Receptor Agonists in Dialysis Patients and After Kidney Transplantation

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Abstract

Limited data exists regarding safety and efficacy of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in patients with end-stage kidney disease (ESKD) on dialysis and in kidney transplant recipients with diabetes. The only randomized trial available has shown that liraglutide did not significantly decrease hemoglobin A1c (HbA1c) levels and increased risk of hypoglycemia in patients with type 2 diabetes on hemodialysis.

Retrospective studies suggested that intake of GLP-1 RAs in dialysis patients with diabetes decreased body weight, HbA1c levels, and complications related to arteriovenous fistula (AVF). Moreover, use of GLP-1 RAs reduced all-cause mortality by 23-37% after a median follow-up of 1.4 to 1.7 years. As result of their beneficial effects on weight and glycemic control, GLP-1 RAs improved the chance of obese dialysis patients to be on waitlisting for kidney transplantation. In kidney-transplant recipients, users of GLP-1 RAs had lower rates of kidney graft loss (7.5% versus 12.2% in non-users) and mortality 13.5% versus 19.9% in non-users). While safety profile of GLP-1 RAs in dialysis patients appeared to be like non-dialysis subjects, the frequency and severity of their adverse effects might be higher in the former group with discontinuation rates of 17-26%. Overall, GLP-1 RAs may have many beneficial effects in patients on dialysis and in kidney transplant recipients. Randomized trials dedicated to hemodialysis patients and kidney transplant recipients with diabetes are urgently needed to determine efficacy and safety of GLP-1 RAs.

Key Words: dialysis; GLP-1 receptor agonists; kidney transplant recipients; arterio-venous graft; mortality; safety

Introduction

GLP-1 RA are underused among patients on dialysis and kidney transplant recipients in large part because these patients were excluded from clinical trials and to a lesser extent because of the limited pharmacokinetic data of GLP-1 RA in the setting of dialysis. In a large study based on a worldwide healthcare data, only 2.1% of patients with diabetes were prescribed a GLP-1R agonist at dialysis initiation [1]. The FLOW trials showed that semaglutide decreased cardiovascular (CV) and kidney events in patients with type 2 diabetes and chronic kidney disease (CKD) [2]. However, subjects with ESKD and those on dialysis were excluded from the FLOW trial [2]. Similarly, in the AWARD-7 trial comparing dulaglutide with insulin glargine in patients with type 2 diabetes and moderate-to-severe CKD, subjects on dialysis were excluded [3]. The American Diabetes Association (ADA) recently recommended that individuals on dialysis can be safely initiated or continued GLP-1 based medications not cleared by the kidneys to reduce CV risk and mortality [4].

Indeed, GLP-1 RAs are presumed to be degraded by proteolytic enzymes into peptides and aminoacids and not cleared by kidneys [5-7]. Meanwhile, there are few studies exploring the pharmacokinetics of GLP-1 RA in dialysis patients. Thus, one small pharmacokinetic study by Jacobsen et al [8] suggested that plasma liraglutide exposure in a small group of 6 on continuous peritoneal dialysis was not significantly altered from subjects with normal kidney function after receiving a single dose of 0.75 mg of liraglutide. Prescribing information of dulaglutide stated that ESKD did not have clinically relevant effects on dulaglutide systemic exposure; maximum plasma concentration (Cmax) being increased by 11% compared with subjects with normal kidney function [6]. Regarding semaglutide, in a single dose study of 10 subjects on hemodialysis, systemic exposure of subcutaneous semaglutide was not significantly different from subjects with normal kidney function after receiving a single small dose of 0.5 mg [8]. Likewise, renal impairment does not seem to impact the pharmacokinetics of the dual agonist of receptors of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) tirzepatide. In fact, the manufacturer does not recommend any dose changes in ESKD [7], the main purpose of this article is to review the effects of GLP-1 RAs in patients with ESKD on dialysis and in kidney transplant recipients based on limited available data.

Data from randomized trials: liraglutide

The only randomized trial exploring the effects of a GLP-1 RA in patients with diabetes on dialysis was a small trial from Denmark by Idorn et al [9]. These authors randomized patients with type 2 diabetes and ESKD (n=24) and control subjects with type 2 diabetes and normal kidney function (n=23) to receive liraglutide (max dose 1.8 mg/d) or placebo. The primary outcome was the difference in dose-corrected trough plasma concentrations of liraglutide between patients and control subjects. After 12 weeks of therapy, liraglutide plasma concentrations were increased by 49% in patients with ESKD versus control individuals [9]. These results were in contrast with those of the pharmacokinetic study mentioned earlier by Jacopbsen et al [8] most likely because of different study protocol. Thus, Idorn et al [9] used higher doses of liraglutide (up to 1.8 mg/d) for 12 weeks, whereas Jacobsen et al [8] employed a single smaller dose of liraglutide of 0.75 mg/d. Clearly, the randomized trial by Idorn et al [9] is more clinically relevant and implies that liraglutide use may not be safe in patients with ESKD. In support of this notion was the increase in gastrointestinal (GI) adverse effects and hypoglycemia in the liraglutide group. Among patients with ESKD randomized to liraglutide, there was a nonsignificant decrease in mean hemogl;obin A1c (HbA1c) values of 0.5% compared with placebo (P=0.71) [9]. Likewise, liraglutide use achieved mean weight loss of 2.4 kg in patients with ESKD that did not reach statistical significance compared with baseline (P=0.22). Meanwhile, in the control group receiving liraglutide, there was significant weight loss at 12 weeks of 2.9 kg (P-=0.03) [9].

Taken together, liraglutide use in patients with diabetes and ESKD did not provide significant benefits in terms of weight loss and glycemia control and increased risk of hypoglycemia.

Data from retrospective studies of various GLP-1 RAs

In a national cohort American study, Orandi et al [10] compared total mortality (study primary outcome) in patients with diabetes taking GLP-1 RA versus non-GLP-1RA users over a median duration of 1.7 years. The types of GLP-1 RA were dulaglutide in 41.8% of subjects, semaglutide in 28.4% and liraglutide in 22.4% [10]. After adjustment of confounding factors, GLP-1 RA use was associated with 23% lower mortality compared with non-users; adjusted hazard ratio (HR) 0.77 (95% CI, 0.70 to 0.85; P< 0.001) [10]. In addition, GLP-1R users lost 4.0 kg compared with a weight loss of 1.5 kg in non-users. This led to a 66% higher chance of kidney transplant waitlisting, adjusted HR: 1.66 (95% CI, 1.28 to 2.13; P< 0.001) [10].

In another cohort study of patients with type 2 diabetes, Lai et al [1] compared mortality (primary outcome) and CV events (secondary outcome) at initiation of hemodialysis between patients prescribed a GLP-1 RA with those prescribed a long-acting insulin within 3 months after dialysis commencement. The GLP-1 RAs used were dulaglutide by 42.4% of patients, semaglutide by 24.9% and liraglutide by 22.0% [1]. Propensity score matching identified 1682 GLP-1 RA users and similar number of long-acting insulin users. After a median duration of 1.4 years, the all-cause mortality was 37% lower among GLP-1RA users versus insulin users; adjusted HR 0.63 (95% CI, 0.50 to 0.80, P<0.001) [1]. Moreover, there was a significant decrease in major CV events: (adjusted HR 0.63, 95% CI, 0.51 to 0.82) and kidney events (defined as remaining in dialysis for 3 years or death); adjusted HR 0.75 (95% CI, 0.64 to 0.87); P< 0.001 for both CV and kidney outcomes compared with long-acting insulin users [1].

Retrospective studies of the GLP-1 RA semaglutide

Two retrospective studies, summarized in table 1, examined efficacy and safety of semaglutide in patients with ESKD, mostly with type 2 diabetes. In both studies, semaglutide was associated with reduction in weight and HbA1c values, although the 0.61% reduction in HbA1c values did not reach statistical significance in the study of Long et al [11] likely due to small number of subjects (n=12). Interestingly, the study by Wade et al [12] was the only study in which semaglutide dose was escalated to 2.0 mg/week achieved in 16 patients (44%) [12. Meanwhile, 6 patients (16.7%) discontinued semaglutide due to GI adverse effects (table 1). Of note, patients on peritoneal dialysis tolerated semaglutide less than those on hemodialysis, with discontinuation rates of 30.8% and 8.7%, respectively [12].

Effects of GLP-1 RA on complications of the arteriovenous fistula

The AVF required for hemodialysis delivery is often complicated by thrombosis and stenosis leading to failure of hemodialysis access. In a retrospective study based on data from the global TriNetX Research Network, Hsu et al [13] compared the effects of GLP-1 RA intake on AVF complications in a cohort of patients (n=1,239) who started a GLP-1RA within 3 months of AVF creation and similar number of control subjects not using GLP-1RA. Most patients (93%) had diabetes [13]. After propensity score matching, at 1 year, the use of GLP-1RA was associated with significant reduction in risk of the following fistula complications: thrombosis (HR 0.77; 95% CI, 0.60 to 0.97), stenosis (HR 0.82; 95% 0.71 to 0.95), infection (HR 0.61; 95% CI, 0.41 to 0.90), dialysis catheter intervention (HR 0.63, 95% CI, 0.53 to 0.76) and open revision (HR 0.57, 95% CI, 0.47 to 0.69) [13]. Furthermore, at 3 years of follow-up, the group of patients receiving GLP-1RA had improved survival (HR 0.81; 95% CI, 0.68 to 0.96) [13]. The mechanisms underlying these beneficial effects on AVF and mortality associated with use of GLP-1 RA are unclear but might be related to amelioration of vascular remodeling within the endothelium and to the anti-atherosclerosis effects of GLP-1 RA [14].

Effects of GLP-1 RA on waitlisting for kidney transplantation

The presence of obesity in ESKD hinders access to kidney transplantation because of increased post-operative complications [15]. Therefore, GLP-1RAs were evaluated as a method of weight loss to improve candidacy for kidney transplant. In one prospective study by Navaux et al [16], 23 obese subjects (mean age 55 years, 61% men, and 15 had type 2 diabetes) received semaglutide up to 1 mg/week. After a median 12.2 months, weight decreased by 11.4 kg from 102.9 to 91.5 kg, BMI by 3.9 points from 35.6 to 31.7 kg/m^2 and waist circumference by 9.6 cm from 119.5 to 109.1 cm [16]. As result of this positive response to semaglutide, 56.5% of patients initially rejected for kidney transplantation were listed within a median of 5.4 months, and 61.5% of them got kidney transplantation.

In the study of Waide et al [12], 48 % of patients who were ineligible for transplant achieved waitlisting activation due to weight loss (table 1) [12].

Use of GLP-1 RA in kidney transplant recipients

Like the situation in hemodialysis, there is remarkable underuse of GLP-1 RA in kidney transplant recipients only taken by 10.9% in the USA [17].

In the largest available retrospective study, Orandi et al [17] used data from the US Renal Data System (URDS) to study the graft survival and total mortality among kidney transplant recipients who received a GLP-1 RA and had pre-existing type 2 diabetes. The most commonly used GLP-1RA was dulaglutide, used by 49% of patients. The 5-year unadjusted graft loss was 7.5% and 12.2% among GLP-1 RA users (n=1969) and non-users (n=16047), respectively, P<0.0001 [17]. In addition, the 5-year unadjusted cumulative incidence for mortality was 13.5% for GLP-1RA users and 19.9% for non-users (P<0.0001) [17]. Of note, the difference in graft survival and mortality remained significant after adjustment for pertinent covariates [17]. In another smaller retrospective study from Isreal (n=272), Cohen et al [18], examined the effects of using GLP-1 RA on a composite kidney outcome formed of graft rejection, start of dialysis, re-transplantation, or all-cause mortality in kidney transplant recipients with diabetes. The types of GLP-1 RA were dulaglutide (used by 52%), liraglutide (29%) and semaglutide (19%) [18]. During a median 3.1-year follow-up, compared with matched control subjects not using GLP-1 RA, there was significant decrease in the kidney outcome among GLP-1RA users (HR 0.49; 95% CI, 0.27 to 0.90) [18]. In addition, at 1 year follow-up, HbA1c levels decreased by 0.5% and 0.1% among GLP-1 RA users and control subjects, respectively (P=0.01) [18]. Body mass index decreased by 0.9 kg/m^2 among GLP-1 RA users versus an increase of 0.3 kg/m^2 among non-users (P=0.01) [18].

Safety of GLP-1 RA in dialysis patients and kidney transplant recipients

In general, the types of adverse effects of GLP-1 RAs in patients on dialysis or in kidney transplant recipients are similar to control subjects. However, the frequency and severity of these adverse effects may be more pronounced in patients on dialysis. Thus, GI adverse effects of liraglutide were significantly more common in patients with ESKD compared to the control subjects with normal kidney function [9]. The higher plasma concentrations of liraglutide in patients with ESKD may explain these increased adverse effects in the group of patients with ESKD [9]. In addition, hypoglycemic events with glucose values between 54-70 mg/dl occurred more frequently in the liraglutide group compared with the placebo group, 58 events in 19 subjects compared with 22 events in 13 subjects, respectively (P=0.02) [9]. In the cohort study of Lai et al [1], there was a 33% increased risk of hypoglycemia among GLP-1 RA users compared with insulin users that did not reach statistical significance; adjusted HR 1.33; (95% CI, 0.94 to 1.88, P=0.12) [1].

Among kidney transplant recipients, increased diabetic retinopathy emerged as an adverse effect among GLP-1 RA users compared with non-users with an adjusted HR of 1.49 (95% CI, 1.11 to 2.00, P=0.008) [17]. Unfortunately, hypoglycemia was not included in this large study as a safety outcome [17]. Discontinuation of the GLP-1 RA due to adverse effects in dialysis patients ranged from 17 to 28% in retrospective studies (table 1), which was higher than corresponding rates in randomized trials of non-dialysis patients. For example, in the FLOW trial including patients with CKD and type 2 diabetes, discontinuation rates of semaglutide (1 mg/week) were 13.2% versus 11.9% with placebo [2].

	Long [11]	Wade [12]
Design	Retrospective	Retrospective
Subjects	n=12 (11 on HD, 1 on PD), age 57, 70% men, BMI 34.8 kg/m^2	N=36, age 54, 46% men, with obesity BMI 39.4 kg/m^2 vs control subjects on lifestyle (2 patients received dulaglutide in 2 patients liraglutide)
Patients with type 2 diabetes	100%	91.7%
Follow-up	Median 17.4 months	1 year
Semaglutide maximum dose	1 mg sc qweek (n=10), 14 mg po qday (n=2)	2 mg sc qweek in 44% of patients (n=16)
Effect on weight	-5.1 kg (95% CI, -8.4 to -1.9) vs baseline (P=0.003)	-9.3Kg vs -3.5 kg in lifestyle-only (P< 0.01)
Effect on HbA1c	-0.61% (95% CI, -1.7 to 0.54) NS	-0.6%
Discontinuation rates due to GI adverse effects	28%	17%
Percentage of patients with hypoglycemia	46%	11%
Comments		48% of patients achieved waitlist activation for kidney transplantation at 1 year, 37% of patients discontinued insulin.

Abbreviations in table 1. HD: hemodialysis, PD: peritoneal dialysis, BMI: body mass index, sc: subcutaneously, HbA1c: glycated hemoglobin, GI: gastrointestinal, NS: non-significant.

Table 1: Semaglutide use in patients with end-stage kidney disease on dialysis.

Conclusions and Clinical Implications

Based on above data, the use of GLP-1 RAs may provide several advantages in dialysis patients, mild weight loss and amelioration of glycemic control, and reduction in mortality and complications of AVF. In addition, in kidney transplant recipients, improved graft survival was a possible another benefit. Patients who are likely to get the most benefit from the GLP-1 RAs are obese patients with diabetes. On the other hand, there are still concerns about increasing risk of hypoglycemia and diabetic retinopathy with use of GLP-1 RAs. Clearly, randomized trials are required to define efficacy, safety and optimum doses of GLP-1 RAs in the setting of dialysis and after kidney transplant.

Conflict of interest

The author has no conflict of interest to declare.

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