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Effects Of Tirzepatide On Kidney Function and Outcomes In Patients With Type 2 Diabetes

Research Article

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Abstract

Background: Recent data suggest that tirzepatide may have kidney protective effects.
Objective: To provide an appraisal of the renal effects of tirzepatide.
Methods: Pubmed search until October 27, 2022. Search terms were tirzepatide, kidneys, albuminuria, diabetes, GIP, GLP-1 agonists. Pertinent clinical trials and reviews were included.
Results: SURPASS-4 trial was a randomized trial comparing efficacy and safety of tirzepatide versus insulin glargine in patients with type 2 diabetes. A post-hoc analysis of SURPASS-4 compared renal outcomes between the 2 treatment modalities. This analysis showed that, compared with insulin glargine, tirzepatide slowed progression of kidney disease by decreasing the decline in estimated glomerular filtration rate (eGFR). During 104 weeks of follow-up, the mean eGFR slope was -1.4 ml/min/1.73 m^2 per year and -3.6 ml/min/1.73 m^2 per year in the tirzepatide group and the insulin group, respectively; between-group difference 2.2 (95% CI 1.6-2.8). Tirzepatide effect on eGFR was more pronounced in patients with baseline eGFR < 60 ml/min/1.73 m2 compared with those with eGFR ≥60 ml/min/1.73 m^2. Urine albumin creatinine ratio (UACR) remained relatively stable in the tirzepatide group but increased progressively in the insulin group. During the 104 weeks of follow-up, UACR was decreased by 31.9% (95% CI 37.7 to 25.7) with tirzepatide versus insulin glargine. Tirzepatide reduced the risk of a composite kidney outcome by 42% compared with insulin glargine; hazard ratio (HR) 0.58, 95% CI 0.43-0.80; P =0.0008). This effect was mainly driven by reduction in new-onset albuminuria. Secondary analyses of trials of glucagon-like peptide-1 (GLP-1) agonists also showed that these agents might have beneficial kidney actions.
Conclusions: Preliminary data suggest that tirzepatide may exert several kidney protective effects in patients with type 2 diabetes. These effects should be examined as primary outcomes in clinical trials including patients with wide spectrum of renal function at baseline.

Keywords: Tirzepatide; type 2 Diabetes; Kidney; Albuminuria; GLP-1 Agonists.

Introduction

Tirzepatide (LY3298176) is a dual receptor agonist of the 2 incretin hormones: glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) that was initially introduced as anti-diabetic agent [1]. Tirzepatide (Mounjaro) was approved in May 2022 by the Federal Drug Administration (FDA) based on a series of phase 3 clinical trials called SURPASS-1 through 5 [1, 2]. SURPASS-4 was an open-label, randomized multinational trial comparing the efficacy and safety of tirzepatide with insulin glargine in patients with type 2 diabetes and high cardiovascular (CV) risk [3]. Study results showed superiority of the 3 doses of tirzepatide (5,10,15 mg once weekly) over insulin glargine (mean dose at 52 weeks 43.5 units/d) in terms of reduction in hemoglobin A1c (HbA1c) levels, body weight, systolic blood pressure (SBP), and frequency of hypoglycemia. However, tirzepatide was less tolerated than insulin glargine with treatment discontinuation rates of 9-11% versus 5% with glargine, mainly due to gastrointestinal adverse effects [3]. Heerspink et al [4] performed a post-hoc analysis of SURPASS-4 trial focusing on kidney effects of tirzepatide versus insulin glargine over a median duration of follow-up of 85 weeks. The study had 2 composite kidney outcomes. The first consisted of time to first occurrence of eGFR decline of ≥40%, death due to kidney failure, progression to end-stage kidney disease (ESKD), or new onset macroalbuminuria (UACR >300 mg/g). The second composite kidney outcome was similar

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to the first but excluded new onset macroalbuminuria [4]. This analysis represents the only available data with respect to the renal effects of tirzepatide. Overview and main results of this post-hoc analysis of SURPASS-4 trial are summarized in table 1 and discussed further below.

Effects Of Tirzepatide On Glomerular Filtration Rate

Tirzepatide slowed the rate of worsening of renal function with time as reflected by the slope of decline of eGFR. Thus, during the 104 weeks follow-up, the mean eGFR slope was -1.4 ml/min/1.73 m^2 per year in the tirzepatide group and -3.6 ml/min/1.73 m^2 per year in the insulin group, between-group difference 2.2 (95% CI 1.6-2.8) [4]. Importantly, tirzepatide effect on eGFR was more pronounced in patients with baseline eGFR < 60 ml/min/1.73 m^2 compared with those with eGFR ≥60 ml/min/1.73 m^2, i.e participants with worse prevalent kidney function got more benefit [4]. Meanwhile, the renal protective effects of tirzepatide were independent of use of other agents known to slow kidney disease such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor blockers (ARB), and sodium-glucose co-transporter-2 (SGLT2) inhibitors [4]. However, in the first 12 weeks after randomization, the fall in eGFR was more evident in the tirzepatide group than in the insulin group [4]. In fact, this acute initial dip in eGFR was also demonstrated with use of other renoprotective agents such as ARB, SGLT2 inhibitors, and the non-steroidal aldosterone antagonist finerenone [5-7]. The exact cause of this early transient decline in eGFR is unclear but is believed to be linked to long-term kidney protection [5].

Effects Of Tirzepatide On Albuminuria

Inspection of the time curves of UACR in the insulin glargine and tirzepatide groups showed that maximum reduction of UACR with tirzepatide was observed at 42 weeks (approximately 20% reduction) followed by gradual rebound to attain a non-significant reduction of 4.4% after 102 weeks. On the other hand, UACR progressively increased from baseline in the insulin glargine group to reach a 56.7% increase at 104 weeks [4]. Overall, during the 104 weeks of follow-up, the between-group difference in UACR was -31.9% (95% CI -37.7 to -25.7) in favor of tirzepatide [4]. In addition, tirzepatide decreased the likelihood of progression to more severe stages of albuminuria [4]. Thus, the HR for worsening UACR stage for tirzepatide versus insulin was 0.43 (95% CI 0.27-0.70) [4]. Conversely, patients assigned to tirzepatide had greater likelihood of regression from microalbuminuria (UACR 30-300 mg/g) to normal UACR or from macroalbuminuria to either microalbuminuria or normal UACR, HR 1.93 (95% 1.51-2.57) [4].

Effects Of Tirzepatide On Kidney Outcomes

Compared with insulin glargine, tirzepatide reduced the risk of the first composite kidney outcome by 42% (HR 0.58, 95% CI 0.43-0.80; P =0.0008) [4]. This effect was mainly driven by reduction in new-onset albuminuria. This conclusion was based on

Table 1. Overview of post-hoc analysis of SURPASS-4 trial and renal outcomes with tirzepatide therapy [4].

	Tirzepatide	Insulin glargine
Patients' number and gender and mean age (years)	N=995, 39% women, 63.4	N= 1,000, 36% women, 63.8
Race	81% Whites, 4% Blacks	83% Whites, 3% Blacks
Proportions of patients with established CV disease	87%	87%
Baseline HbA1c levels	8.54%	8.50%
Baseline eGFR (ml/min/1.73 m^2)	81.1	81.5
Proportions of subjects with eGFR <60ml/min/1.73 m^2	18%	17%
Proportions of patients with microalbuminuria (UACR 30-300 mg/g)	28%	27%
Proportions of patients with macroalbuminuria (UACR > 300 mg/g)	8%	8%
Proportions of patients using RAS blockers	81%	81%
Proportions of patients using SGLT-2 inhibitors	25%	26%
Slope of eGFR during the 104 weeks follow-up	-1.4 ml/min/1.73 m^2 per year; difference vs placebo 2.2 (95% CI 1.6-2.8)	-3.6 ml/min/1.73 m^2 per year
UACR during the 104 weeks follow-up	-6.8% (-14 to 1.1), difference vs placebo -31.9% (95% CI 37.7 to -25.7)	36.9% (95% 26.0 to 48.7)
HR of tirzepatide vs glargine in first composite kidney outcome *	0.58, 95% CI 0.43-0.80; P =0.0008	
HR of tirzepatide vs glargine in second composite kidney outcome**	0.80 (95% CI 0.52-1.22; P = 0.321	

Values are means

Abbreviations: CV: cardiovascular, eGFR; estimated glomerular filtration rate, UACR: urine-albumin creatinine ratio, RAS: renin angiotensin system, SGLT2: sodium-glucose co-transporters 2, HR: hazard ratio

* first occurrence of eGFR decline of ≥40%, death due to kidney failure progression to ESKD, or new onset macroalbuminuria (UACR >300 mg/g).

**similar to first outcome after exclusion of macroalbumunuria.

the fact that the effect of tirzepatide on the second composite kidney outcome that excluded new onset macroalbuminuria was no longer significant, HR 0.80 (95% CI 0.52-1.22; P =0.321) [4].

Mechanisms Of Renal Effects Of Tirzepatide

The mechanisms of tirzepatide renal beneficial effects are not fully understood but are likely multifactorial. The significant decrease of hemoglobin A1c values, body weight and SBP by tirzepatide are likely among the reasons [3]. However, the relative contribution of these factors is unclear because adjustment for changes in HbA1c levels and weight did not change the results [4]. However, adjustment for changes in SBP was not reported [4]. A direct effect of tirzepatide on the kidneys cannot be excluded. That the renal effects of tirzepatide remained unchanged regardless of use of ACEI, ARB or SGLT2 inhibitors suggest that the underlying mechanisms of renoprotection of tirzepatide were different from those agents [4].

Effects of GLP-1 agonists on kidney function

Several clinical trials evaluated the effects of GLP-1 agonists on renal function as secondary outcomes [8]. In a meta-analysis of 6 large trials, Sattar et al [8] showed that GLP-1 agonists reduced kidney outcomes by 21% (HR 0.79; 95% CI 0.73-0.87, P<0.0001). These outcomes were a composite that consisted of new onset macroalbuminuria, doubling of serum creatinine or a least a 40% decline in eGFR, kidney replacement therapy or death due to kidney disease [8]. Moreover, after excluding the short-acting GLP-1 agonist lixisenatide, treatment with GLP-1 agonists decreased worsening kidney function (defined as either doubling of serum creatinine or ≥40% decline in eGFR) by 18% (HR 0.82; 95% CI 069-098, P=0.03) [8].

In an exploratory analysis of the REWIND trial (n=9,901, mean eGFR 76.9 ml/min/1.73 m^2) with median follow-up of 4.5 years, Gerstein et al [9] evaluated renal outcomes of the GLP-1 agonist dulaglutide. These outcomes were a composite of new onset macroalbuminuria, a sustained decline in eGFR of ≥30% or renal replacement therapy [9]. Thus, dulaglutide therapy was associated with reduction in this composite outcome versus placebo; HR 0.85 (95% CI 0.77-0.93, P=0.0004) [9]. Interestingly, in terms of the individual components of the renal outcome, the clearest effect of dulaglutide was the decrease in new onset macroalbuminuria; HR 0.77 (95% CI, 0.68-0.87; P< 0.0001) [9]. Similarly, in the LEADER trial, Mann et al [10] reported that liraglutide decreased the renal composite outcome (new onset macroalbuminuria, doubling of serum creatinine, ESKD, or death due to renal disease) versus placebo, HR 0.78 (95% CI 0.67-0.92; P=0.003). Again, this decrease in the renal outcome was driven primarily by the significant reduction of macroalbuminuria, HR 0.74 (95% 0.60-0.91; P=0.004) [10]. In a recent analysis of the LEADER trial and SUSTAIN-6 trial of semaglutide, Shaman et al [11] showed that the kidney-protective effects of liraglutide and semaglutide were more pronounced in patients with pre-existing chronic kidney disease (CKD) having eGFR < 60 ml/min/1.73 m^2.

Conclusions And Current Needs

Post-hoc analysis of SURPASS-4 trial suggests for the first time that tirzepatide may delay progression of diabetic nephropathy by slowing the decline in eGFR and decreasing albuminuria. These observations were primarily recorded in patients with type 2 diabetes and relatively preserved kidney function. It is essential therefore to confirm these results in adequately powered randomized studies across a wide spectrum of baseline kidney function. Likewise, secondary analysis of trials of different GLP-1 agonists suggest that these agents may exert renal protective effects. The FLOW trial is a large (n=3,508) randomized trial underway to evaluate the kidney effects of the GLP-1 agonist semaglutide versus placebo in patients with type 2 diabetes and CKD [11]. The primary outcome in FLOW is the composite of kidney failure, a persistent ≥50% reduction in eGFR, and kidney or CV death [11]. Confirmation of renal protection by tirzepatide and GLP-1 agonists will constitute another advantage of these agents in addition to their established efficacy in glycemic control and weight loss.

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