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ORIGINAL RESEARCH

Tirzepatide Prescribing Practices and Efficacy in Patients with Diabetes and Chronic Kidney Disease at a Large Tertiary Care Center in the United States

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Purpose: Chronic kidney disease is a frequent complication of diabetes mellitus. Tirzepatide is the first dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist approved for glycemic control in patients with type 2 diabetes. We present the efficacy and prescribing practices of tirzepatide in a cohort with diabetes and chronic kidney disease in a large tertiary care setting.

Methods: We retrospectively identified new outpatient tirzepatide prescriptions in adults ≥18 years with diabetes and chronic kidney disease stages 1–5 from 2022 to 2023 across the Barnes Jewish Hospital system (St Louis, Missouri).

Results: We identified 102 subjects with chronic kidney disease and diabetes who started tirzepatide between 2022 and 2023, and used for ≥6 months. Mean duration of tirzepatide use in our cohort was 13.89 ± 2.51 months. Among subjects who stopped, 57% (n=4) were due to limited medication availability or lack of insurance coverage. Tirzepatide use led to a significant reduction in hemoglobin A1c by 1.15%, weight by nearly 10%, systolic and diastolic blood pressure, and total cholesterol ($p<0.05$ for all).

Conclusion: We found that tirzepatide was an effective therapy with significant benefits on glycemic control, blood pressure, cholesterol, and weight in subjects with diabetes and chronic kidney disease treated at a tertiary care facility.

Keywords: chronic kidney disease, diabetes, tirzepatide, incretin

Introduction

Chronic kidney disease is a frequent complication of diabetes mellitus, occurring in 20–50% of individuals with type 2 diabetes.[1] In recent years, there have been advancements for the treatment of chronic kidney disease and type 2 diabetes, including approval of the non-steroidal mineralocorticoid receptor antagonist, finerenone, and sodium-glucose cotransporter-2 inhibitors. These present significant progress in the therapeutic landscape of chronic kidney disease in type 2 diabetes by targeting different mechanisms. Current guidelines from the Kidney Disease Improving Global Outcomes Workgroup in 2022 recommend the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for patients with diabetes and albuminuric chronic kidney disease.[2] Finerenone or sodium-glucose cotransporter-2 inhibitors can be additional therapeutic options for patients with type 2 diabetes and estimated glomerular filtration rate ≥25 mL/min per 1.73 m^2 or ≥20 mL/min per 1.73 m^2, respectively.[2] Incretin therapy, including glucagon-like peptide-1 receptor agonists, is recommended for glycemic control and cardiovascular risk reduction, but none are currently approved for direct treatment of chronic kidney disease outcomes. Evaluation of secondary renal outcomes for several glucagon-like peptide-1 receptor agonists including semaglutide and dulaglutide showed promise in reducing composite renal outcomes.[3] However, renal outcomes were not the primary endpoints in these studies. To fill this gap, FLOW is

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a randomized, double-blind, phase 3b trial of semaglutide 1.0 mg in patients with type 2 diabetes and chronic kidney disease, which evaluated the primary composite renal outcome of kidney failure, at least a 50% reduction in estimated glomerular filtration rate, or death from kidney or cardiovascular causes.[4] The trial was terminated early due to meeting efficacy endpoints with a 24% reduction in the prespecified composite outcome compared to placebo.[5] Therefore, incretins remain a potential therapy to improve kidney outcomes in patients with type 2 diabetes and chronic kidney disease.

Tirzepatide is the first dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist approved for glycemic control in patients with type 2 diabetes. In the SURPASS 4 study, tirzepatide produced a greater reduction in hemoglobin A1c with a lower risk of hypoglycemia compared to insulin glargine.[6] Furthermore, tirzepatide use led to a greater reduction in hemoglobin A1c, fasting glucose level, and body weight compared to semaglutide in the SURPASS 2 study.[7] A pooled analysis of SURPASS trials further showed that tirzepatide increased the odds of achieving normoglycemia by 16 times compared to control.[8] There has not been a study evaluating tirzepatide use in kidney outcomes as a primary endpoint in subjects with type 2 diabetes and chronic kidney disease. However, a post-hoc analysis of the SURPASS 4 trial found that tirzepatide use led to a lower decline in the annual estimated glomerular filtration rate and reduced the composite kidney endpoint defined as an estimated glomerular filtration rate decline greater than 40% from baseline, renal death, kidney failure, or new-onset macroalbuminuria (HR 0.58, 95% CI 0.43–0.8).[9] The ability of tirzepatide to reduce albuminuria is important, which recent studies have shown to be a prognostic marker in patients with diabetes. Albuminuria has been shown to increase all-cause mortality in addition to cardiovascular mortality.[10] There have been no real-world studies, to our knowledge, evaluating prescribing practices and efficacy of tirzepatide in a cohort only with diabetes and chronic kidney disease to date. This is important to confirm how results from randomized controlled trials translate to a clinical setting. Furthermore, understanding prescribing practices can provide a better understanding of potential challenges faced by prescribers or patients, and inform future studies to improve patient care. To meet this need, we present the efficacy and prescribing practices of tirzepatide in a cohort with diabetes and chronic kidney disease in a large tertiary care setting.

Methods

This is a retrospective observational cohort study to assess the prescribing practices and clinical efficacy of tirzepatide use in patients with diabetes and chronic kidney disease. The primary outcome is to understand prescribing practices including provider specialty who provided the tirzepatide prescription, reason for prescription, duration of use, maximum dose tolerated, alternative glucagon-like peptide-1 receptor agonists before or switched to after tirzepatide, and why tirzepatide was stopped. Secondary outcomes include clinical outcomes such as patient reported side effects and change in hemoglobin A1c, weight loss, estimated glomerular filtration rate, urine albuminuria, blood pressure, and cholesterol (LDL, total cholesterol).

This study was approved by the Washington University Institution Review Board. This study was in compliance with the Declaration of Helsinki. Data was de-identified before analysis. We retrospectively identified new outpatient tirzepatide prescriptions in adults ≥18 years with diabetes and chronic kidney disease stages 1–5 from 2022 to 2023 across the Barnes Jewish Hospital system (St Louis, Missouri). Inclusion criteria included patients ≥18 years, type 2 diabetes and chronic kidney disease stages 1–5 with or without albuminuria, and confirmed tirzepatide use for ≥6 mos. Exclusion criteria included age <18 years, pregnancy, tirzepatide use <6 mos or never filled prescription based on patient report, or absence of chronic kidney disease or diabetes. Patients were also excluded if there was significant missing data due to not receiving diabetes care in our healthcare system, which precludes the ability to assess outcomes. The definition of type 2 diabetes was identified based on ICD-10 code with further confirmation from provider notes, hemoglobin A1c, and c-peptide, where available. Chronic kidney disease stages were defined based on CKD-EPI 2021 criteria after a review of labs. One subject had latent autoimmune diabetes in adulthood, but had intact c-peptide and was included since the subject was managed as having type 2 diabetes. The charts of all eligible patients were manually reviewed to determine eligibility based on inclusion/exclusion criteria above.

Data Collection

We extracted baseline demographic data, concomitant medications, specialty of provider, reason for prescription, stopping, or switching, patient-reported side effects, and clinical outcomes over this period (hemoglobin A1c, estimated glomerular filtration rate, weight or body mass index, blood pressure, LDL or total cholesterol, urine albuminuria).

Statistical Analysis

Continuous variables were presented as mean ± standard deviation, and categorical variables as the number and proportion. Normality was tested by Shapiro–Wilk or Kolmogorov–Smirnov test.

Continuous variables were assessed by paired t-test or its nonparametric equivalent Wilcoxon signed-rank test. Changes in estimated glomerular filtration rate, systolic or diastolic blood pressure, cholesterol (LDL, total cholesterol), weight, hemoglobin A1c, urine albumin–creatinine ratio, and body mass index were compared at baseline to last value in the specified period. Analyses were completed with GraphPad PRISM version 10.0.1 or Microsoft Excel. The results were significant if $p < 0.05$.

Results

Of 427 subjects, 325 were not included. A total of 193 of these subjects used tirzepatide for <6 months or did not start due to lack of insurance coverage or medication availability. Three subjects did not have diabetes, 2 subjects did not have tirzepatide prescriptions, and 47 did not actually have chronic kidney disease based on estimated glomerular filtration rates in the specified period. Furthermore, 80 subjects could not be used due to significant missing data (Figure 1). From these, we identified 102 subjects with chronic kidney disease and diabetes who started tirzepatide between 2022 and 2023, and used for ≥6 months who met inclusion criteria. The mean duration of tirzepatide use in our cohort was 13.89 ± 2.51 months (Table 1). The mean age of patients was 61.16 ± 10.06 years. Our cohort was 57% female (n=58), and 43% male (n=44). Seventy-five percent of the cohort was white (n=76), 2% identified as other (n=2), 23% identified as black (n=24), and 1% (n=1) was Hispanic. Ninety-nine percent (n=101) of patients had type 2 diabetes, and 1% (n=1) had latent autoimmune diabetes of adulthood who was managed as a subject with type 2 diabetes. At the time of tirzepatide initiation, 7% (n=7) had chronic kidney disease stage 1, 33% (n=34) stage 2, 53% (n=54) stage 3, 5% (n=5) stage 4, and 2% (n=2) stage 5. The mean duration of diabetes was 14.75 ± 8.27 years, and chronic kidney disease 9.86 ± 7.28 years. Additional complications include neuropathy in 63% (n=64) and cardiovascular disease in 34% (n=35). From our cohort, 70% (n=71) had concomitant angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, while 40% (n=41) had sodium-glucose cotransporter-2 inhibitor use, and 1% (n=1) used finerenone.

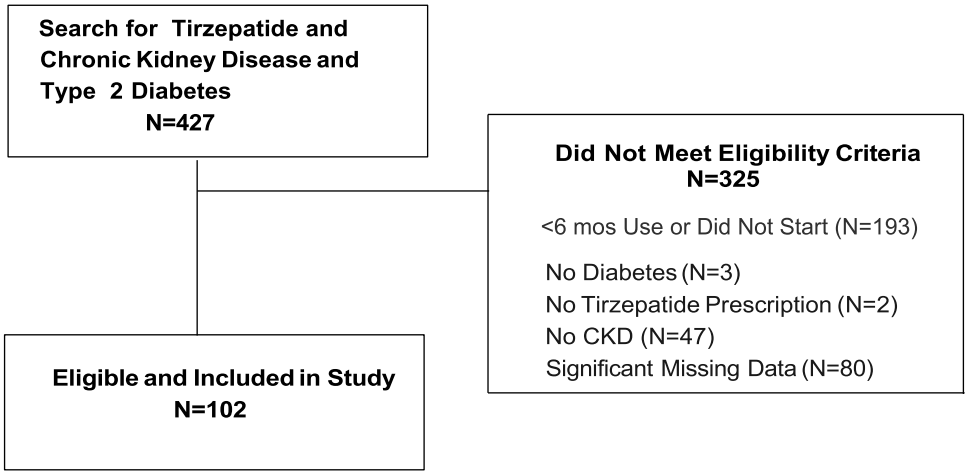

Figure 1 Subjects Included in Study.

Table 1 Baseline Patient Characteristics

	N=102 (%)
Gender	
Male	44 (43%)
Female	58 (57%)
Race	
White/Caucasian	76 (75%)
Black	24 (23%)
Other	2 (2%)
Ethnicity	
Non-Hispanic	101 (99%)
Hispanic	1 (1%)
Mean Duration of Tirzepatide Use (Months ± SD)	13.89 ± 2.51
Age (years ± SD)	61.16 ± 10.06
Baseline Hemoglobin A1c	7.69 ± 1.52%
Duration of (years ± SD)	
CKD	9.86 ± 7.28 years
Diabetes	14.75 ± 8.27 years
Other Diabetes Complications	
Neuropathy	64 (63%)
Cardiovascular disease	35 (34%)
Concomitant Medications	
ACEI/ARB	
Yes	71 (70%)
No	31 (30%)
SGLT2i	
Yes	41 (40%)
No	61 (60%)
Finerenone	
Yes	1 (1%)
No	101 (99%)
Baseline CKD Stage	
1	7 (7%)
2	34 (33%)
3	54 (53%)
4	5 (5%)
5	2 (2%)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker, CKD, chronic kidney disease; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

Next, we evaluated the characteristics of tirzepatide prescriptions. The most common reason for tirzepatide initiation was glycemic control in 66% (n=67) of patients, 33% (n=34) started for weight loss, and the reason for starting was not able to be identified in 1% (n=1) (Table 2). The majority of patients were switched from an existing glucagon-like peptide-1 receptor agonist in 55% (n=56) with most subjects switching from dulaglutide in 59% (n=33) or subcutaneous semaglutide in 35% (n=20). Less commonly, patients were switched from liraglutide, oral semaglutide, or insulin glargine-lixisenatide. Sixty percent (n=61) of tirzepatide was prescribed by endocrinologists, while 33% (n=34) or 6%

Table 2 Characteristics of Tirzepatide Prescribing

Reason for Starting Tirzepatide	**N=102 (%)**
Glycemic Control	67 (66%)
Weight Loss	34 (33%)
Unknown	1 (1%)
Prescribing Specialties	
Endocrine	61 (60%)
Primary Care	34 (33%)
Weight loss clinic	6 (6%)
Unknown	1 (1%)
Incretin Prescriptions Prior to Tirzepatide N=56 (55%)	
Dulaglutide	33 (59%)
Liraglutide	1 (2%)
Semaglutide (SQ)	20 (35%)
Insulin glargine-lixisenatide	1 (2%)
Semaglutide (Oral)	1 (2%)
Maximum Tirzepatide Dose Achieved	
2.5 mg	3 (3%)
5 mg	16 (16%)
7.5 mg	18 (18%)
10 mg	23 (22%)
12.5 mg	17 (17%)
15 mg	25 (24%)

Abbreviation: SQ, subcutaneous.

(n=6) were prescribed by primary care and weight loss clinic providers, respectively. Twenty-four percent (n=25) of patients reached a maximum dose of 15 mg, 17% (n=17) reached 12.5 mg, and 22% (n=23) were treated with 10 mg. Only 19% (n=19) remained at lower doses of either tirzepatide 2.5 or 5 mg. In terms of discontinuation, 7% (n=7) of subjects stopped tirzepatide after a mean duration of 8.29 ± 1.98 months. Among the subjects who stopped, 57% (n=4) were due to lack of medication availability or insurance coverage, while 29% (n=2) stopped due to nausea/vomiting.

Next, we assessed the primary outcomes of tirzepatide on glycemic control and weight loss in subjects with chronic kidney disease. The mean baseline hemoglobin A1c was 7.69 ± 1.52%, which decreased by 15% to a mean hemoglobin A1c of 6.54 ± 0.89% ($p<0.05$) (Figure 2). From our cohort, 19% achieved normoglycemia with a mean hemoglobin A1c of ≤5.7%. Furthermore, mean weight decreased by nearly 10% from a mean baseline of 116.81 ± 29.56 to 106.84 ±

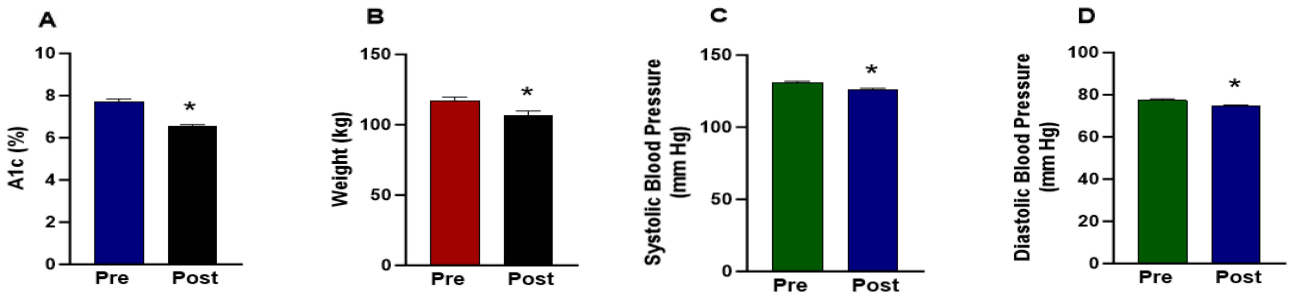

Figure 2 Tirzepatide Reduces Hemoglobin A1c, Weight, and Blood Pressure.
Notes: Assessment of clinical measures at baseline and after Tirzepatide use: (**A**) hemoglobin A1c (**B**) weight (**C**) systolic blood pressure (**D**) diastolic blood pressure.

29.46 kg ($p<0.05$). Subjects experienced a decrease in body mass index from 43.98 ± 22.89 to 38.45 ± 8.25 kg/m^2 ($p<0.05$).

We also evaluated secondary outcomes of tirzepatide use on blood pressure, cholesterol, and renal function. Use of tirzepatide led to a decrease in systolic blood pressure by 4.85 mm Hg from 130.72 ± 11.71 to 125.87 ± 12.54 mm Hg ($p<0.05$). There was also a significant reduction in diastolic blood pressure from 77.25 ± 7.79 to 74.52 ± 7.24 mm Hg ($p<0.05$). There was no significant change in the estimated glomerular filtration rate after tirzepatide use with a baseline estimated glomerular filtration rate of 57.92 ± 20.17 to 56.18 ± 20.32 mL/min per 1.73 m^2 ($p=0.08$). Of 74 patients with cholesterol levels, there was no significant difference in LDL. Finally, of 80 subjects, tirzepatide reduced total cholesterol 5.7% from 149.31 ± 39.75 to 140.78 ± 37.06 mg/dl ($p<0.05$). There were too few subjects in our cohort with corresponding labs before and after tirzepatide use to assess the effect on albuminuria.

Twenty percent (n=20) of the total cohort experienced side effects, the most common of which was mild gastrointestinal such as nausea/vomiting or constipation in 90% (n=18). Two subjects experienced serious side effects, one with cholecystitis and another with small bowel obstruction, after which tirzepatide was resumed. Of 20% of subjects (n=20) who developed hypoglycemia, 25% (n=5) had level 1, 45% (n=9) level 2, no subjects experienced level 3 hypoglycemia, and 30% (n=6) had hypoglycemia of an undefined severity. Seventy-five percent (n=15) of those who had hypoglycemia were on insulin and 5% (n=1) were on a sulfonylurea.

Discussion

We present the effect and prescribing practices of tirzepatide in patients with diabetes and chronic kidney disease stages 1–5. In this population, we confirmed that tirzepatide use significantly reduced hemoglobin A1c by 1.15% and produced a nearly 10% reduction in weight after a mean duration of 13.89 months compared to baseline. Furthermore, tirzepatide use significantly reduced systolic blood pressure by 3.7% and diastolic blood pressure by 3.5%. Therapy also led to a significant reduction in total cholesterol, but there were no significant changes in estimated glomerular filtration rate or LDL through this period. In terms of prescribing practices, we found tirzepatide was prescribed more frequently by endocrinologists than primary care providers for glycemic control. Prior to starting tirzepatide, more patients were switched from dulaglutide or semaglutide than other glucagon-like peptide-1 receptor agonists. We found tirzepatide was generally well-tolerated, with mild gastrointestinal symptoms being the most common. Only 2 patients experienced more serious events (cholecystitis, small bowel obstruction), both of whom resumed tirzepatide after the event. Hypoglycemia was generally mild without any episodes of level 3 hypoglycemia requiring external assistance.

The results of our study provide additional real-life data to existing SURPASS clinical trials of tirzepatide in subjects with type 2 diabetes. First, we found a significant reduction in hemoglobin A1c of 1.15%. In SURPASS 1, a 40-week trial of tirzepatide compared to placebo, tirzepatide therapy reduced hemoglobin A1c by −1.87, −1.89, −2.07% for 5 mg, 10 mg, or 15 mg doses, respectively.[11] Furthermore, in a meta-analysis of all SURPASS 1–5 trials, tirzepatide use reduced hemoglobin A1c by −1.55% at 5 mg to −1.87% at the 15 mg dose.[12] The glycemic reduction is more modest in our study compared to these clinical trials. Furthermore, 19% of subjects achieved normoglycemia with a hemoglobin A1c ≤5.7% in our study, which is modest compared to a recent study that showed tirzepatide increased the odds of achieving normoglycemia by 16-fold.[8] This difference may reflect differences in study methodology, and our results need to be confirmed in larger real-world studies. Our results support the finding that tirzepatide provides robust glycemic benefits in a population with diabetes and chronic kidney disease. Tirzepatide therapy also produced a 9.97 kg weight loss, which is the mean from all tirzepatide doses (2.5 to 15 mg). This is near the upper end of the weight loss range from SURPASS 1, which showed tirzepatide reduced weight by 7 kg at the 5 mg dose to 9.5 kg at the 15 mg dose or 9.81 kg composite loss in a systematic review of tirzepatide studies.[11,12] This supports the efficacy of tirzepatide for patients outside of clinical trials, even with continued use of medications that enhance weight gain such as insulin or sulfonylureas.

Tirzepatide has also been shown to have cardiometabolic benefits. A systematic review of randomized clinical trials showed tirzepatide significantly improved systolic and diastolic blood pressure in addition to total cholesterol, LDL, and HDL.[13] We also found tirzepatide produced a 4.87 mm Hg systolic blood pressure reduction, which is consistent with the 4.2 to 5.77 mm Hg reduction in the SURPASS studies.[13] Furthermore, the 5.7% reduction in total cholesterol in our study

is consistent with the higher end found in clinical trials, though we did not find a significant reduction in LDL with tirzepatide use.[13] This difference may be due to inadequate power in our study since we had LDL data in only a subset of subjects. In terms of the effect of tirzepatide on other diabetes complications, a recent study did not show an increase in the risk of retinopathy.[14] We were unable to determine the effect on retinopathy from our cohort as many patients received annual screenings outside of our healthcare system, and the results were not adequately documented in our health records. Finally, the nonsignificant 1.74 mL/min per 1.73 m^2 reduction in the estimated glomerular filtration rate was consistent with the 1.4 mL/min per 1.73 m^2 annual reduction in the post-hoc analysis of renal outcomes in SURPASS 4.[9]

We found tirzepatide was generally well-tolerated in patients with chronic kidney disease and diabetes, though even in our small cohort there were 2 serious events during treatment previously reported with glucagon-like peptide-1 receptor agonist therapy. Larger real-world studies are needed to define the risk of serious events with tirzepatide use. Also, we found an episode of hypoglycemia in 20% of the cohort, the majority of whom were on either insulin or sulfonylureas. Therefore, it is vital for physicians to make appropriate dose reductions, if needed, when starting tirzepatide in patients on insulin or sulfonylureas.

In terms of prescribing practices, most prescriptions were initiated by endocrinologists compared to primary care physicians. This may reflect a need for enhanced provider familiarity with tirzepatide for primary care providers. Our discontinuation rate was 7%, which is at the higher end of the SURPASS 1 study, which had a dose-dependent increase in the discontinuation rate from 3% at 5 mg to 7% at 15 mg due to gastrointestinal side effects.[11] However, in our study, of those who stopped tirzepatide, the majority were due to lack of coverage or medication availability. This is also seen in the initial review of all subjects of which many were excluded from the study as the patients were prescribed tirzepatide, but were unable to start due to lack of insurance coverage or limited medication availability. Furthermore, from our cohort, 75% (n=76) of the subjects on tirzepatide were white, which may reflect disparities in access to novel diabetes medications. We highlight the importance of enhancing medication coverage and availability to improve care for patients with chronic kidney disease and diabetes.

Our study had several limitations. First, due to the retrospective nature, medication adherence was solely dependent on patient reports, which could not be confirmed with pharmacy history or insurance claims. Another limitation is the lack of adjustment for confounders such as the addition of other medications, which can influence clinical outcomes. Furthermore, the observational nature inherently leads to missing data, which may bias the results and reduce the power of our study. Our study was also of a shorter duration, so whether these findings will hold in a longer setting is unknown. Finally, since our study cohort is small and limited to a single institution, its generalizability may be limited. Future studies need to be conducted in patients with diabetes and chronic kidney disease to confirm the benefits of tirzepatide for kidney outcomes.

In conclusion, we found tirzepatide was an effective therapy with significant benefits on glycemic control, blood pressure, total cholesterol, and weight in subjects with diabetes and chronic kidney disease treated at a tertiary care facility. However, we found barriers to patient access to tirzepatide during the study period. Expansion of coverage and medication availability needs to be improved to ensure equitable access to all patients.

Data Sharing Statement

De-identified data can be made available upon request to the corresponding author.

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Disclosure

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