

Duration of GLP-1 Receptor Agonist Therapy and Nephrolithiasis Risk in Type 2 Diabetes: A Multicenter Retrospective Cohort Study

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Abstract

Purpose

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) improve glycemic control and metabolic health, but their association with nephrolithiasis remains poorly defined. We evaluated the relationship between GLP-1 RA exposure duration and incident nephrolithiasis among adults with type 2 diabetes mellitus (T2DM).

Methods

Using the TriNetX Research Network, adults with T2DM were stratified according to GLP-1 RA exposure as no exposure, < 1 year, 1–3 years, or 3–5 years. Patients with chronic kidney disease, prior nephrolithiasis, bariatric surgery, or prior sodium-glucose cotransporter-2 inhibitor exposure were excluded. Pairwise propensity score matching and time-to-event analyses were performed. Two complementary analyses were conducted: a broader T2DM cohort evaluating nephrolithiasis risk across GLP-1 RA exposure durations and a secondary cohort restricted to patients with at least 5 years of established T2DM.

Results

In the broader T2DM cohort, shorter GLP-1 RA exposure was associated with higher nephrolithiasis risk. No exposure was associated with greater risk than < 1 year of exposure (HR 1.037, 95% CI 1.010–1.065; $p = 0.006$), < 1 year was associated with greater risk than 1–3 years (HR 1.071, 95% CI 1.008–1.138; $p = 0.028$), and 1–3 years was associated with greater risk than 3–5 years (HR 1.189, 95% CI 1.075–1.315; $p = 0.001$). In the cohort restricted to patients with at least 5 years of T2DM, no significant differences were observed among the longer GLP-1 RA exposure-duration comparisons, indicating the absence of a progressive duration-response relationship in patients with established diabetes.

Conclusion

Longer GLP-1 RA exposure was associated with lower nephrolithiasis risk in the broader T2DM population. However, this duration-response relationship was not observed among patients with at least 5 years of established T2DM. These findings suggest that the association between GLP-1 RA exposure duration and nephrolithiasis may differ according to diabetes chronicity and warrant prospective investigation.

Introduction

Nephrolithiasis is a common urologic condition with a rising global incidence and is estimated to affect approximately 10–15% of the population during their lifetime.¹ The burden of kidney stone disease has increased over recent decades, with epidemiologic studies demonstrating growing prevalence in parallel with metabolic disorders such as obesity and type 2 diabetes mellitus (T2DM).² Patients with T2DM are at increased risk of nephrolithiasis due to metabolic abnormalities, including insulin resistance-associated reductions in urinary pH and increased uric acid supersaturation.³ These metabolic changes predispose individuals with diabetes to both uric acid and calcium-containing stones and contribute to higher recurrence rates compared with the general population.³

Glucagon-like peptide-1 (GLP-1) receptor agonists have become an increasingly important class of medications in the management of T2DM because of their ability to improve glycemic control while promoting weight loss and cardiovascular risk reduction.⁴ Large randomized clinical trials have demonstrated that GLP-1 receptor agonists such as liraglutide and dulaglutide significantly reduce major cardiovascular events in patients with diabetes.^{4,5} In addition to these cardiometabolic benefits, emerging evidence suggests that GLP-1 receptor agonists may also exert Reno-protective effects through mechanisms including natriuresis, improved endothelial function, and reductions in systemic inflammation.⁶

Despite these benefits, the potential influence of GLP-1 receptor agonists on nephrolithiasis risk remains poorly understood. Antidiabetic medications may alter urinary chemistry and metabolic pathways that contribute to kidney stone formation, making it clinically important to evaluate their impact on stone disease.³ Given the close relationship between obesity, insulin resistance, and nephrolithiasis, therapies that improve metabolic health may influence stone risk.² However, data examining the association between GLP-1 receptor agonist therapy and kidney stone formation are limited.

Increasing attention has been directed toward how different classes of antidiabetic medications may influence nephrolithiasis risk through their effects on metabolic and urinary parameters. Patients with T2DM are known to have a higher risk of kidney stone formation due to insulin resistance-associated reductions in urinary pH and increased uric acid supersaturation.^{1,2} Epidemiologic studies have also demonstrated differences in stone composition and metabolic risk profiles among patients with metabolic disease.³ More recently, sodium–glucose cotransporter-2 (SGLT2) inhibitors have been associated with a lower risk of kidney stone formation in several observational studies, potentially due to osmotic diuresis and increased urinary volume that may reduce lithogenic supersaturation.⁷ Large population-based analyses have similarly reported reduced nephrolithiasis incidence among patients with T2DM treated with SGLT2 inhibitors compared with other glucose-lowering therapies.⁸

In contrast, the effects of other antidiabetic medications on kidney stone risk remain less well defined. While improved glycemic control may theoretically reduce stone risk through correction of metabolic abnormalities associated with diabetes, the direct impact of specific medication classes remains uncertain.^{1,2} GLP-1 receptor agonists have attracted growing interest because of their effects on weight

reduction, metabolic regulation, and renal physiology. Emerging studies evaluating patients receiving GLP-1–based therapies have begun to explore changes in urinary stone risk factors, though findings remain limited and sometimes inconsistent.⁹ As the clinical use of GLP-1 receptor agonists continues to expand for the treatment of both diabetes and obesity, further investigation is needed to clarify their potential impact on nephrolithiasis risk.

Some studies evaluating urinary metabolic profiles in patients receiving GLP-1 based therapies have reported inconsistent changes in stone risk parameters, and population-level analyses examining antidiabetic medications have produced conflicting findings.⁸ Given the expanding use of GLP-1 receptor agonists for the management of T2DM and obesity, clarifying their potential association with kidney stone formation has important clinical implications. Therefore, this study aimed to evaluate the relationship between the duration of GLP-1 receptor agonist therapy and the risk of kidney and ureteral stones among adults with T2DM using a large multicenter electronic health record database.

Methods

Data Collection

TriNetX, an international federated health research network that provides access to de-identified electronic medical record data from participating healthcare institutions, was utilized for this study at the Penn State College of Medicine, Department of Urology, in Hershey, Pennsylvania. The dataset was obtained from the TriNetX Research Network in April 2026. TriNetX does not provide users with protected health information (PHI) or personally identifiable information. Only aggregated data and statistical summaries derived from de-identified records are available through the platform. All analyses were conducted within the TriNetX web-based analytics interface using data spanning the preceding 20 years. No formal patient consent was required. TriNetX complies with the Health Insurance Portability and Accountability Act (HIPAA) and the General Data Protection Regulation (GDPR). This study qualified for exemption from institutional review board (IRB) review because the data meet the de-identification standards outlined in § 164.514(a) of the HIPAA Privacy Rule.

Study Population and Cohort Definitions

Adults aged ≥ 18 years with a diagnosis of type 2 diabetes mellitus (T2DM) were identified within the TriNetX Research Network and evaluated for glucagon-like peptide-1 receptor agonist (GLP-1 RA) exposure and subsequent nephrolithiasis. Patients were stratified according to GLP-1 RA exposure duration as no exposure, < 1 year, 1–3 years, or 3–5 years.

Two complementary cohort analyses were performed. The first analysis included the broader population of adults with T2DM and evaluated nephrolithiasis risk across increasing durations of GLP-1 RA exposure. The second analysis was restricted to patients with at least 5 years of established T2DM, defined by a qualifying healthcare encounter occurring at least 5 years after the initial T2DM diagnosis.

This secondary analysis was performed to evaluate whether the association between GLP-1 RA exposure duration and nephrolithiasis differed among patients with longer-standing diabetes.

Patients with chronic kidney disease, nephrolithiasis before the index date, bariatric surgery, or prior sodium-glucose cotransporter-2 inhibitor (SGLT2i) exposure were excluded.

Pairwise propensity score matching was performed between GLP-1 RA exposure-duration cohorts. Comparisons included no GLP-1 RA exposure versus < 1 year of exposure, < 1 year versus 1–3 years of exposure, 1–3 years versus 3–5 years of exposure, and < 1 year versus 3–5 years of exposure. Matching variables included demographic characteristics, including age, sex, race, and ethnicity, as well as baseline diagnoses and medication categories.

Outcome Variables

The primary outcome was incident nephrolithiasis following the index date. For each analysis, the index date was defined as the earliest date on which a patient met all prespecified eligibility and exposure criteria applicable to that cohort. For patients in the GLP-1 RA exposure groups, exposure duration was determined according to the prespecified duration category at the time the applicable cohort criteria were satisfied. In the secondary analysis restricted to patients with established T2DM, patients were additionally required to have a qualifying healthcare encounter occurring at least 5 years after their initial T2DM diagnosis.

Time-to-event analyses were performed to evaluate the association between GLP-1 RA exposure duration and subsequent nephrolithiasis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were used as the primary measures of association.

Data Analysis

Baseline demographic and clinical characteristics were assessed between matched cohorts. Continuous variables were reported as mean $\pm$ standard deviation, and categorical variables were reported as number and percentage. Covariate balance following propensity score matching was assessed using standardized mean differences (SMDs), with lower SMD values indicating greater balance between cohorts.

The TriNetX platform was used to perform time-to-event analyses and calculate HRs with corresponding 95% CIs for nephrolithiasis across GLP-1 RA exposure-duration cohorts. Analyses were performed separately for the broader T2DM population and the cohort restricted to patients with at least 5 years of established T2DM. An alpha level of 0.05 was used as the threshold for statistical significance.

Results

Baseline Characteristics

Following propensity score matching, baseline characteristics were well balanced across pairwise comparisons in the cohort of patients with at least 5 years of established T2DM. Pairwise matched cohorts included no GLP-1 RA exposure versus < 1 year of exposure, < 1 year versus 1–3 years of exposure, 1–3 years versus 3–5 years of exposure, and < 1 year versus 3–5 years of exposure.

For the no GLP-1 RA exposure versus < 1 year comparison, each matched cohort included 117,174 patients, with a mean age of 58.5 ± 13.6 years in both groups. The < 1 year versus 1–3 years comparison included 60,605 patients per group, while the 1–3 years versus 3–5 years comparison included 41,675 patients per group. The < 1 year versus 3–5 years comparison included approximately 41,682 patients per group. Across these comparisons, mean age ranged from 57.4 to 57.9 years, female patients represented approximately 61%–63% of each cohort, White individuals represented approximately 66%–67%, and Black or African American individuals represented approximately 20%.

Overall, standardized mean differences were low after propensity score matching, indicating adequate covariate balance between comparison groups. No clinically meaningful differences were observed in demographic characteristics, cardiovascular disease history, endocrine or metabolic diagnoses, or baseline medication categories. Baseline characteristics of the matched cohorts are summarized in Table 1.

No GLP-1 medication use vs < 1 year GLP-1 medication use

Characteristic	No GLP-1	< 1 year GLP-1	P value	SMD
Age, years (mean ± SD)	58.5 ± 13.6	58.5 ± 13.6	0.978	< 0.001
Sex, n (%)				
Male	46,359 (39.6)	46,339 (39.5)	0.933	< 0.001
Female	70,751 (60.4)	70,746 (60.4)	0.983	< 0.001
Race, n (%)				
White individuals	77,258 (65.9)	77,237 (65.9)	0.927	< 0.001
Black or African American individuals	23,457 (20.0)	23,443 (20.0)	0.942	< 0.001
Asian individuals	3,599 (3.1)	3,612 (3.1)	0.876	0.001
American Indian or Alaska Native individuals	966 (0.8)	986 (0.8)	0.649	0.002
Native Hawaiian or Other Pacific Islander individuals	860 (0.7)	863 (0.7)	0.942	< 0.001
Ethnicity, n (%)				
Hispanic or Latino individuals	11,103 (9.5)	11,142 (9.5)	0.783	0.001
Not Hispanic or Latino individuals	89,552 (76.4)	89,524 (76.4)	0.892	0.001
Diagnosis, n (%)				
Diseases of the circulatory system	99,158 (84.6)	99,140 (84.6)	0.918	< 0.001
Endocrine, nutritional and metabolic diseases	117,174 (100)	117,174 (100)	--	--
Medication, n (%)				
Blood glucose regulation agents	107,318 (91.6)	107,324 (91.6)	0.964	< 0.001
Hormones, synthetics, or modifiers	112,632 (96.1)	112,630 (96.1)	0.983	< 0.001
Cardiovascular medications	107,301 (91.6)	107,295 (91.6)	0.964	< 0.001

< 1 year GLP-1 medication use vs 1–3 year GLP-1 medication use

Characteristic	< 1 year GLP-1	1–3 year GLP-1	P value	SMD
Age, years (mean ± SD)	57.5 ± 13.1	57.4 ± 13.2	0.106	0.009
Sex, n (%)				
Male	23,309 (38.5)	23,363 (38.5)	0.750	0.002
Female	37,267 (61.5)	37,207 (61.4)	0.723	0.002
Race, n (%)				
White individuals	40,447 (66.7)	40,295 (66.5)	0.355	0.005
Black or African American individuals	12,285 (20.3)	12,229 (20.2)	0.689	0.002
Asian individuals	1,989 (3.3)	2,082 (3.4)	0.138	0.009
American Indian or Alaska Native individuals	414 (0.7)	459 (0.8)	0.126	0.009
Native Hawaiian or Other Pacific Islander individuals	438 (0.7)	502 (0.8)	0.036	0.012
Ethnicity, n (%)				
Hispanic or Latino individuals	4,918 (8.1)	5,056 (8.3)	0.149	0.008
Not Hispanic or Latino individuals	45,834 (75.6)	45,645 (75.3)	0.207	0.007
Diagnosis, n (%)				
Diseases of the circulatory system	52,929 (87.3)	52,854 (87.2)	0.518	0.004
Endocrine, nutritional and metabolic diseases	60,605 (100)	60,605 (100)	--	--
Medication, n (%)				
Blood glucose regulation agents	60,605 (100)	60,605 (100)	--	--
Hormones, synthetics, or modifiers	60,605 (100)	60,605 (100)	--	--
Cardiovascular medications	58,177 (96.0)	58,045 (95.8)	0.056	0.011

1–3 year GLP-1 medication use vs 3–5 year GLP-1 medication use

Characteristic	1–3 year GLP-1	3–5 year GLP-1	P value	SMD
Age, years (mean ± SD)	57.9 ± 12.4	57.9 ± 12.4	0.475	0.005
Sex, n (%)				
Male	15,456 (37.1)	15,526 (37.3)	0.616	0.003
Female	26,200 (62.9)	26,115 (62.7)	0.543	0.004
Race, n (%)				
White individuals	27,831 (66.8)	27,594 (66.2)	0.082	0.012
Black or African American individuals	8,460 (20.3)	8,493 (20.4)	0.776	0.002
Asian individuals	1,503 (3.6)	1,507 (3.6)	0.941	0.001
American Indian or Alaska Native individuals	206 (0.5)	255 (0.6)	0.022	0.016
Native Hawaiian or Other Pacific Islander individuals	252 (0.6)	277 (0.7)	0.276	0.008
Ethnicity, n (%)				
Hispanic or Latino individuals	3,086 (7.4)	3,052 (7.3)	0.652	0.003
Not Hispanic or Latino individuals	30,751 (73.8)	30,610 (73.4)	0.268	0.008
Diagnosis, n (%)				
Diseases of the circulatory system	36,840 (88.4)	36,651 (87.9)	0.043	0.014
Endocrine, nutritional and metabolic diseases	41,675 (100)	41,675 (100)	--	--
Medication, n (%)				
Blood glucose regulation agents	41,675 (100)	41,675 (100)	--	--
Hormones, synthetics, or modifiers	41,675 (100)	41,675 (100)	--	--
Cardiovascular medications	40,372 (96.9)	40,264 (96.6)	0.035	0.015

< 1 year GLP-1 medication use vs 3–5 year GLP-1 medication use

Table 1
Baseline characteristics of matched type 2 diabetes mellitus cohorts by duration of GLP-1 receptor agonist exposure.

Characteristic	< 1 year GLP-1	3–5 year GLP-1	P value	SMD
Age, years (mean ± SD)	57.9 ± 12.3	57.9 ± 12.4	0.521	0.004
Sex, n (%)				
Male	15,501 (37.2)	15,526 (37.2)	0.858	0.001
Female	26,164 (62.8)	26,121 (62.7)	0.758	0.002
Race, n (%)				
White individuals	27,765 (66.6)	27,594 (66.2)	0.210	0.009
Black or African American individuals	8,484 (20.4)	8,493 (20.4)	0.938	0.001
Asian individuals	1,442 (3.5)	1,507 (3.6)	0.223	0.008
American Indian or Alaska Native individuals	221 (0.5)	256 (0.6)	0.108	0.011
Native Hawaiian or Other Pacific Islander individuals	267 (0.6)	277 (0.7)	0.667	0.003
Ethnicity, n (%)				
Hispanic or Latino individuals	3,078 (7.4)	3,053 (7.3)	0.740	0.002
Not Hispanic or Latino individuals	30,673 (73.6)	30,610 (73.4)	0.621	0.003
Diagnosis, n (%)				
Diseases of the circulatory system	36,773 (88.2)	36,657 (87.9)	0.215	0.009
Endocrine, nutritional and metabolic diseases	41,682 (100)	41,682 (100)	--	--
Medication, n (%)				
Blood glucose regulation agents	41,682 (100)	41,682 (100)	--	--
Hormones, synthetics, or modifiers	41,682 (100)	41,682 (100)	--	--
Cardiovascular medications	40,310 (96.7)	40,270 (96.6)	0.441	0.005

Baseline demographic, diagnostic, and medication characteristics are shown for patients with type 2 diabetes mellitus for at least 5 years, stratified by GLP-1 medication exposure duration. Pairwise matched comparisons include no GLP-1 medication use vs < 1 year of GLP-1 use, < 1 year vs 1–3 years of GLP-1 use, 1–3 years vs 3–5 years of GLP-1 use, and < 1 year vs 3–5 years of GLP-1 use. Continuous variables are reported as mean ± standard deviation, and categorical variables are reported as number and percentage. Standardized mean differences were used to assess covariate balance between cohorts, with lower values indicating better balance. Cohort 1 and Cohort 2 correspond to the first and

second exposure groups listed in each table title, respectively. GLP-1 = glucagon-like peptide-1; T2DM = type 2 diabetes mellitus; SD = standard deviation; SMD = standardized mean difference.

GLP-1 RA Exposure Duration and Nephrolithiasis Risk in the Broader T2DM Cohort

In the broader T2DM cohort, shorter GLP-1 RA exposure was consistently associated with higher nephrolithiasis risk compared with longer exposure. Patients without GLP-1 RA exposure had a slightly higher risk of nephrolithiasis compared with patients with < 1 year of exposure (HR 1.037, 95% CI 1.010–1.065; $p = 0.006$).

Similarly, patients with < 1 year of GLP-1 RA exposure had a higher risk of nephrolithiasis compared with those with 1–3 years of exposure (HR 1.071, 95% CI 1.008–1.138; $p = 0.028$). Patients with 1–3 years of exposure also had a higher risk compared with those with 3–5 years of exposure (HR 1.189, 95% CI 1.075–1.315; $p = 0.001$). Although the magnitude of the differences was modest, the direction of association was consistent across comparisons, with longer GLP-1 RA exposure associated with a lower risk of nephrolithiasis in the broader T2DM population (Fig. 1).

GLP-1 RA Exposure Duration and Nephrolithiasis Risk Among Patients With at Least 5 Years of T2DM

In the secondary analysis restricted to patients with at least 5 years of established T2DM, the progressive duration-related pattern observed in the broader cohort was not reproduced. A statistically significant difference in nephrolithiasis risk was observed between patients without GLP-1 RA exposure and those with < 1 year of exposure (HR 0.829, 95% CI 0.776–0.886; $p < 0.001$).

However, no statistically significant differences were observed across longer GLP-1 RA exposure durations. Nephrolithiasis risk did not significantly differ between patients with < 1 year and 1–3 years of exposure (HR 1.051, 95% CI 0.955–1.156; $p = 0.308$), between patients with 1–3 years and 3–5 years of exposure (HR 1.055, 95% CI 0.942–1.181; $p = 0.356$), or between patients with < 1 year and 3–5 years of exposure (HR 1.074, 95% CI 0.954–1.197; $p = 0.196$). Thus, unlike the broader T2DM cohort, a progressive association between increasing GLP-1 RA exposure duration and lower nephrolithiasis risk was not observed among patients with at least 5 years of established T2DM (Fig. 2).

Discussion

In this retrospective cohort study of adults with type 2 diabetes mellitus (T2DM), the association between glucagon-like peptide-1 receptor agonist (GLP-1 RA) exposure duration and nephrolithiasis differed according to the population examined. In the broader T2DM cohort, shorter GLP-1 RA exposure was consistently associated with higher nephrolithiasis risk compared with longer exposure, suggesting a possible duration-related association. However, when the analysis was restricted to patients with at least 5 years of established T2DM, this progressive duration-response relationship was not observed. Although a statistically significant difference was present between patients without GLP-1 RA exposure

and those with < 1 year of exposure, comparisons across longer exposure-duration strata were not statistically significant. Taken together, these findings suggest that the relationship between GLP-1 RA exposure duration and nephrolithiasis may differ according to diabetes chronicity rather than representing a uniformly increasing benefit with longer treatment.

These findings are clinically relevant because patients with T2DM are known to have an increased risk of nephrolithiasis. A recent study using NHANES 2007–2020 data estimated kidney stone prevalence among adults with diabetes at 14.3%–16.1%, compared with 8.5%–9.4% among individuals without diabetes, with diabetes associated with 63% higher odds of kidney stones (OR 1.63, $p < 0.001$).¹⁰ This elevated risk is partly attributable to insulin resistance, lower urinary pH, and increased uric acid supersaturation.^{11,12}

Insulin resistance impairs renal ammonium excretion and reduces urinary citrate, leading to unduly acidic urine that promotes uric acid stone formation and may also contribute to calcium-based stone risk.^{11,13}

A cross-sectional NHANES analysis demonstrated that among persons with type 2 diabetes, more severe disease as measured by HbA1c, fasting glucose, and insulin resistance was associated with a heightened risk of kidney stones (OR 2.82 for HbA1c $\geq 6.5\%$ vs. $<5.7\%$).¹⁴

A systematic review and meta-analysis of over 934,000 participants confirmed that metabolic syndrome components including diabetes (OR 1.55), obesity (OR 1.53), hypertension (OR 1.61), and dyslipidemia (OR 1.59) are each independently associated with increased nephrolithiasis risk.¹⁵

GLP-1 RAs improve glycemic control, promote weight loss, and may exert favorable renal and anti-inflammatory effects, providing several plausible mechanisms through which these agents could influence the metabolic environment associated with stone formation. GLP-1 RAs have been reported to reduce HbA1c by approximately 0.4%–1.6% and produce weight loss of approximately 1.5–6.0 kg over 30 weeks of therapy.^{16,17}

Importantly, their potential renal effects may extend beyond improvements in glycemia and weight. A mediation analysis from cardiovascular outcomes trials of liraglutide and semaglutide found that changes in glycemia or blood pressure accounted for only approximately 10%–25% of the observed kidney outcome benefits, suggesting the possibility of additional renal mechanisms.¹⁸ GLP-1 receptors are expressed within the kidney, particularly in endothelial cells and vascular smooth muscle cells of the juxtaglomerular apparatus, and GLP-1 RA administration has been associated with natriuresis, diuresis, and urinary alkalization, potentially through inhibition of the sodium-hydrogen exchanger NHE3 in the proximal tubule.^{18,19}

The duration-related association observed in the broader T2DM population may therefore reflect metabolic changes accompanying GLP-1 RA therapy. Improvements in insulin sensitivity can occur relatively early after initiation of GLP-1 RA therapy, with liraglutide demonstrating improvements within

weeks and before substantial weight loss.^{20,21} Weight loss with GLP-1 receptor agonists is seen as early as four weeks, with a plateau after four to six months.¹⁷ These changes could potentially modify lithogenic factors through improvements in insulin resistance, glycemic control, body weight, systemic inflammation, or renal physiology. However, the observational design of the present study does not allow determination of which, if any, of these mechanisms account for the observed association.

Importantly, the duration-related pattern observed in the broader population was attenuated when the analysis was restricted to patients with at least 5 years of established T2DM. Several explanations are possible. Longer-standing diabetes may be accompanied by greater metabolic disease burden, chronic insulin resistance, cumulative comorbidities, or other physiologic changes that could modify the association between GLP-1 RA exposure and stone formation. Alternatively, differences between the broader and restricted cohorts may reflect treatment selection, medication adherence, disease severity, healthcare utilization, survivorship, or other residual confounding that cannot be fully captured within an electronic health record database. Therefore, the absence of a progressive duration-response relationship in the ≥ 5 -year T2DM cohort should not be interpreted as evidence that GLP-1 RA therapy becomes ineffective with longer-standing diabetes. Rather, it indicates that the association between increasing treatment duration and lower nephrolithiasis risk observed in the broader population was not reproduced after restricting the analysis to patients with established T2DM.

These findings add to a growing body of literature examining how antidiabetic medication classes may influence kidney stone risk. The relationship between GLP-1 RAs and nephrolithiasis remains less well defined than that of some other glucose-lowering therapies. Post hoc analyses of four clinical trials demonstrated that acute exenatide infusion increased urinary uric acid excretion in association with urinary alkalinization, whereas prolonged GLP-1 RA treatment did not result in sustained changes in uric acid clearance or serum uric acid levels.²² These findings suggest that the effects of GLP-1 RAs on urinary stone risk factors may be complex and may not depend on a single metabolic pathway. The present study contributes population-level evidence demonstrating an association between GLP-1 RA exposure duration and nephrolithiasis in adults with T2DM while also demonstrating that this relationship differs when the analysis is restricted to patients with longer-established diabetes.

The present study contributes population-level evidence suggesting that GLP-1 receptor agonist therapy may nonetheless be associated with reduced nephrolithiasis risk among adults with type 2 diabetes, potentially through metabolic pathways distinct from those of SGLT2 inhibitors.

A major strength of this study is the use of the TriNetX Research Network, which provides access to a large, multicenter electronic health record database encompassing more than 110 million patients from approximately 65 healthcare organizations in the United States, including academic medical centers and community hospitals. The network contains detailed clinical information that is harmonized to standardized terminologies and undergoes extensive data quality procedures.²³ The large sample size permitted evaluation of a clinically meaningful outcome across multiple GLP-1 RA exposure-duration groups. Propensity score matching was used to balance demographic characteristics, comorbid disease

categories, and medication exposures across comparison groups. Baseline balance after matching was strong, with generally low standardized mean differences, supporting comparability of the matched cohorts.

This allowed for evaluation of a clinically meaningful outcome across large matched cohorts. Propensity score matching was used to balance demographic characteristics, comorbid disease categories, and medication exposures across comparison groups, including blood glucose regulation agents, cardiovascular medications, endocrine/metabolic diseases, and circulatory system diseases. Baseline balance after matching was strong across the analyzed cohorts, with standardized mean differences generally below accepted thresholds, supporting comparability between groups.

This study also has several limitations. First, its retrospective observational design prevents causal inference. Although propensity score matching was performed, residual confounding remains possible, including differences in obesity severity, glycemic control, diet, hydration status, medication adherence, diabetes severity, healthcare utilization, and other clinical factors not fully captured within the database. These limitations are particularly relevant in pharmacoepidemiologic studies, in which confounding by indication and unmeasured differences between treatment groups may influence observed associations.^{24,25}

Second, TriNetX does not provide detailed information regarding stone composition, imaging confirmation, stone burden, or 24-hour urine chemistry. Therefore, this study cannot determine whether GLP-1 RAs are associated with specific stone subtypes or directly alter urinary risk factors including pH, citrate, calcium, oxalate, uric acid, sodium, or urine volume.⁸ In addition, medication prescriptions recorded in electronic health records do not necessarily confirm adherence or continuous medication use throughout the assigned exposure period.

Exposure-duration analyses may also be influenced by systematic differences between patients who remain on GLP-1 RA therapy for longer periods and those with shorter exposure. Patients contributing to longer-duration cohorts must remain observable and continue therapy long enough to enter those exposure categories and may therefore differ in medication tolerance, follow-up intensity, disease severity, treatment response, or provider prescribing patterns. Such treatment-selection and survivorship effects may partially explain the apparent duration-related association observed in the broader T2DM cohort. The secondary analysis restricted to patients with at least 5 years of established T2DM was intended to evaluate the association within a population with longer-standing disease; however, this restriction does not eliminate residual confounding or other biases inherent to retrospective exposure-duration analyses. Additionally, TriNetX is composed predominantly of academic medical centers, which may limit generalizability to community-based populations and introduce hospital-based selection bias.^{23,26}

Overall, this study suggests that GLP-1 receptor agonist therapy is associated with a reduced risk of nephrolithiasis among adults with type 2 diabetes, with the strongest signal observed after treatment

initiation. While the magnitude of risk reduction was modest, the findings are meaningful given the high prevalence of both type 2 diabetes and kidney stone disease with kidney stone prevalence among diabetic adults reaching 16.1% in recent NHANES data and the estimated annual number of individuals with both conditions approaching 380,000 in the US.¹⁰

Future studies should incorporate medication adherence, diabetes duration and severity, longitudinal glycemic and weight trajectories, imaging-confirmed stone outcomes, stone composition, and 24-hour urine parameters to better characterize the relationship between GLP-1 RA therapy and nephrolithiasis. Prospective studies will be necessary to determine whether GLP-1 RAs directly influence kidney stone risk and whether this relationship is modified by the duration or severity of T2DM.

Conclusions

In this large multicenter retrospective cohort study of adults with type 2 diabetes mellitus, GLP-1 receptor agonist exposure duration was associated with nephrolithiasis risk, although the pattern differed between the populations examined. In the broader T2DM cohort, shorter GLP-1 receptor agonist exposure was consistently associated with higher nephrolithiasis risk compared with longer exposure, suggesting a possible duration-related association. However, among patients with at least 5 years of established T2DM, a progressive reduction in nephrolithiasis risk was not observed across longer exposure-duration strata.

These findings suggest that the relationship between GLP-1 receptor agonist exposure duration and nephrolithiasis may differ according to diabetes chronicity. Given the retrospective observational design, causal inference cannot be established, and residual confounding related to medication adherence, obesity severity, glycemic control, diabetes severity, healthcare utilization, stone composition, imaging confirmation, and urinary metabolic parameters remains possible. Prospective studies incorporating longitudinal metabolic data, medication adherence, imaging-confirmed stone outcomes, stone composition, and 24-hour urine chemistry are needed to clarify whether GLP-1 receptor agonist therapy directly influences nephrolithiasis risk and whether this relationship is modified by the duration of T2DM.

Declarations

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Author Contribution

L.O. conceived the project, contributed to data collection and analysis, drafted the manuscript, and prepared the figures. A.K. contributed to data collection and assisted with drafting the Introduction. A.N. contributed to data analysis and interpretation, drafted the Results section, and prepared the figures. A.D.

contributed to data collection, assisted with drafting the Methods section, and prepared the figures. S.N. contributed to drafting the Conclusion and portions of the Discussion. L.K. provided clinical interpretation and advised on the clinical relevance of the findings. A.S.A. supervised the project, provided overall scientific and clinical guidance, and advised on the clinical relevance and interpretation of the findings. All authors critically reviewed the manuscript and approved the final version.

Data Availability

The data analyzed in this study were obtained from the TriNetX Research Network, a federated health research network containing de-identified electronic health record data from participating healthcare organizations. The underlying patient-level data are maintained by TriNetX and participating institutions and are not publicly available or directly accessible for distribution by the authors. Aggregate data supporting the findings of this study are presented within the manuscript. Access to TriNetX data may be available to eligible researchers through participating institutions or directly through TriNetX, subject to applicable institutional agreements and data-use requirements.

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Figures

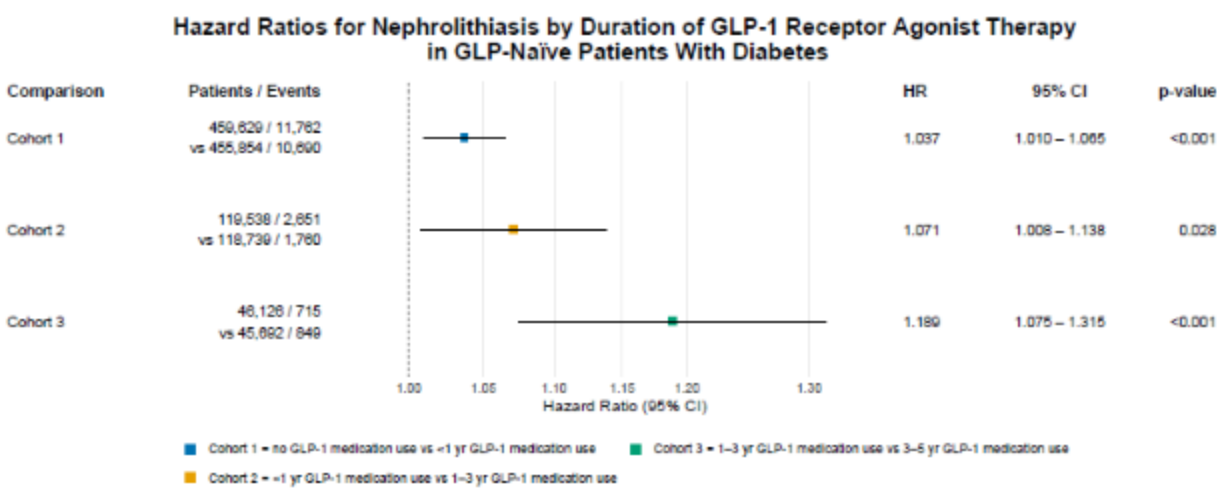


Figure 1

Hazard ratios for nephrolithiasis by GLP-1 receptor agonist exposure duration in the broader type 2 diabetes mellitus cohort. Forest plot demonstrating pairwise comparisons across increasing GLP-1 RA exposure durations, including no exposure versus <1 year, <1 year versus 1–3 years, and 1–3 years versus 3–5 years. Shorter exposure duration was consistently associated with higher nephrolithiasis risk compared with longer exposure. Points represent hazard ratios and horizontal lines indicate 95% confidence intervals.

Hazard Ratios for Nephrolithiasis Following Initiation of GLP-1 Receptor Agonist Therapy in Patients With At Least 5 Years of Diabetes Mellitus

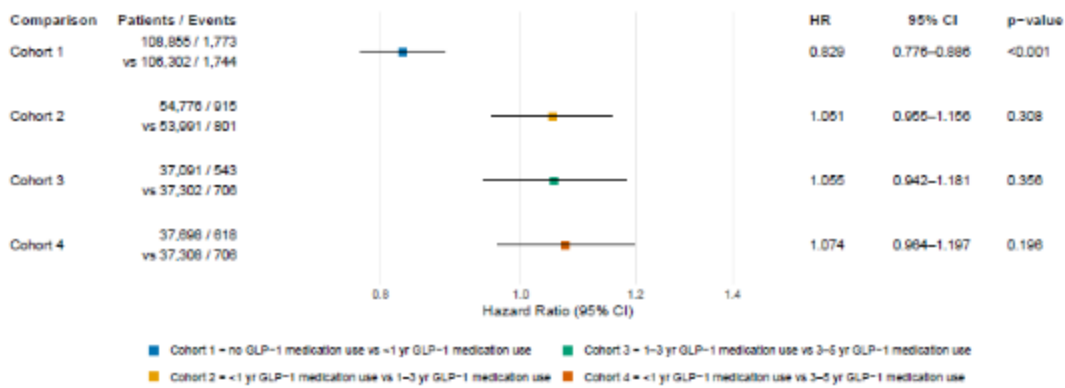


Figure 2

Hazard ratios for nephrolithiasis by GLP-1 receptor agonist exposure duration among patients with at least 5 years of type 2 diabetes mellitus. Forest plot demonstrating pairwise comparisons across various durations post initiation of GLP-1 agonist therapy: no use vs <1 year, <1 year vs 1–3 years, 1–3 years vs 3–5 years, and <1 year vs 3-5 years. GLP-1 receptor agonist exposure for the first year was associated with lower nephrolithiasis risk compared to no exposure. However, after one year, there were no significant differences observed across duration strata. Points represent hazard ratios and horizontal lines indicate 95% confidence intervals.