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RENAL OUTCOMES IN PATIENTS WITH DIABETES MELLITUS ALONE VERSUS DIABETES MELLITUS WITH HYPERTENSION.

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Abstract

OBJECTIVE: Long term renal outcome (estimated glomerular filtration rate (eGFR) reduction, progression of albuminuria, and end-stage renal disease (ESRD) incidence) in T2DM alone group will be compared to those with comorbid T2DM and hypertension. ***MATERIALS AND METHODS***: It was a retrospective observational study with a multi-center electronic health record database from 2018 to 2024. The patients were divided into two groups, Group A: patients with confirmed T2DM; Group B: patients with confirmed T2DM and HTN. The primary outcome was the annualized eGFR slope. The significance level of $p<0.05$ was considered as a statistically significant difference. ***RESULTS***: After PSM, 4,218 patients each were included and followed for a median of 4.8 years. Group B exhibited a significantly steeper annualized eGFR decline compared to Group A (-3.82 ± 1.1 vs. -1.94 ± 0.8 mL/min/1.73m^2/year, $p < 0.001$). The risk of progression to macroalbuminuria was significantly greater in Group B. Furthermore, the composite renal outcome occurred in 14.2% of Group B versus 6.8% of Group A. ***CONCLUSION***: Hypertension is an independent and strong risk factor for the progression of renal function and for the development of albuminuria in patients with T2DM. This is a high-risk comorbid group in which aggressive multi-factorial risk factor management is essential with renoprotection agents initiated early.

Keywords: Diabetes Mellitus, Hypertension, Diabetic Kidney Disease, Estimated Glomerular Filtration Rate, Albuminuria, Chronic Kidney Disease.

INTRODUCTION

Diabetes Mellitus (DM) is one of the most challenging problems in public health of the 21st century whose prevalence is increasing exponentially. Diabetes is a global disease affecting more than 530 million adults (and will affect more than 640 million by 2030).1 Nearly 4 are at an exponentially higher risk of developing DKD than those with normotension2 and among the numerous microvascular and macrovascular complications of this metabolic disorder, Diabetic Kidney Disease (DKD) is the single most important cause of chronic kidney disease (CKD) and End-Stage Renal Disease (ESRD) worldwide. Hyperglycemia causes metabolic disturbances such as the production of advanced glycation end-products (AGEs) and stimulation of the polyol pathway directly leading to podocyte and mesangial cell injury.3 At the same time, hypertension exerts a mechanical stress on the glomerular capillaries that results in the development of glomerular hypertension, hyperfiltration and ultimately in barotrauma.4 These two pathological processes combine to drive up activation of the Renin-Angiotensin-Aldosterone System (RAAS) and the sympathetic nervous system. The efferent arteriole is constricted selectively by angiotensin II, a powerful vasoconstrictor which leads to proteinuria.5

In addition, DM and HTN promote the expression of Transforming Growth Factor-beta (TGF-β), which is a master regulator of the deposition of the extracellular matrix, causing glomerulosclerosis and tubulointerstitial fibrosis.6,7 Recent molecular findings have also underscored the importance of oxidative stress and endothelial dysfunction as important mediators within this dual-pathology model, in which endothelial dysfunction-driven by the decrease of nitric oxide bioavailability has a negative effect on insulin resistance and vascular stiffness.8

Although DM and HTN are well known comorbidities of each other at the individual level, there is a critical knowledge gap in the literature that directly compares specific renal outcomes in patients with DM alone vs. those with comorbid DM and HTN within large, real-world cohorts over a long-term follow-up period. Although there are several randomized controlled trials (RCTs) that have tested the effect of individual antihypertensive or antidiabetic medications (e.g., SGLT2 inhibitors or mineralocorticoid receptor antagonists) in mixed populations, few observational studies have carefully separated out the additive prognostic role of hypertension on the natural history of DKD after careful adjustment for other confounding factors.9,10 In order to stratify risk, allocate resources and tailor therapeutic interventions, it is crucial to understand this differential trajectory. Moreover, current clinical guidelines suggest that the target blood pressure should be <130/80 mmHg in people with diabetes to reduce renal risk.11

But the extent to which these targets are achieved and what the actual renal consequences will be in patients with both conditions at baseline, compared with those who remain normotensive, needs to be tested empirically. Hypertension can not only accelerate the decrease in estimated glomerular filtration rate (eGFR) but also change the course of albuminuria from normoalbuminuria to microalbuminuria to macroalbuminuria much more rapidly.12 The primary aim of this study is to compare long-term renal outcome of the patients with Type 2 Diabetes Mellitus alone and with Type 2 Diabetes Mellitus and Hypertension, defined as annualized eGFR decline, progression of albuminuria, and incidence of ESRD, in a large, propensity score-matched population.

MATERIALS AND METHODS

This study used a large, de-identified, electronic health record (EHR) database of more than 150 primary care and specialty clinics from a variety of geographic locations as a retrospective, observational, multi-center cohort study. The study period was from 2018 to 2024, and minimum follow up period per patient was 2 years and maximum was 7 years. The study protocol was written following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and was approved by the Institutional Review Board (IRB) of the coordinating center with informed consent waiver based on the retrospective and de-identified nature of the data. The population pool included all adult patients (age ≥18 years) with a known diagnosis of Type 2 Eligible patients included those who were aged ≥18 years at the index date, had a confirmed diagnosis of T2DM, had baseline eGFR ≥30 mL/min/1.73m² to allow sufficient time for follow up before the onset of ESRD, and had at least 24 months of continuous follow up with at least 3 serum creatinine measurements that were documented at least 6 months apart to calculate a reliable eGFR slope. Exclusion criteria included: (1) diagnosis of Type 1 Diabetes Mellitus (E10.x); (2) pre-existing ESRD or baseline eGFR <30 mL/min/1.73m²; (3) history of primary glomerulonephritis, polycystic kidney disease, or other non-diabetic non-hypertensive primary renal disease; (4) history of kidney transplantation before the index date; and (5) missing baseline laboratory data (HbA1c or urine albumin-to-creatinine ratio [UACR]). Patients who fulfilled the inclusion criteria were separated into two groups: hypertensive and non-hypertensive patients. Group A (T2DM Alone): All patients with a confirmed diagnosis of T2DM (ICD-10 codes E11-E14) with no documented history of hypertension (ICD-10 codes I10-I15), without baseline blood pressure readings ≥140/90 mmHg, and who were not receiving antihypertensive treatment at the index date. Group B (T2DM with HTN): Patients who had been diagnosed with T2DM and had a concurrent or prior diagnosis of essential hypertension (blood pressure ≥140/90 mmHg on at least two separate occasions) or were receiving active treatment with at least one antihypertensive class (e.g., ACE inhibitors, ARBs, calcium channel blockers, thiazide diuretics, or beta-blockers). The baseline demographic and clinical data were obtained from the EHR at the index date (first eligible encounter that met all criteria). The following variables were included: age, sex, race/ethnicity, duration of diabetes, duration of hypertension (for Group B), and smoking. Baseline laboratory parameters included HbA1c, fasting lipid profile (LDL-C, HDL-C, and triglycerides), serum creatinine, eGFR, and UACR. Information obtained at baseline and during follow-up included medications used, including renin-angiotensin-aldosterone system (RAAS) inhibitors (ACEi/ARBs), Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors, Glucagon-Like Peptide-1 (GLP-1) receptor agonists, non-steroidal mineralocorticoid receptor antagonists (e.g., finerenone), and statins. The primary outcome was the annualized eGFR slope (mL/min/1.73m2/year) computed for each patient, based on linear mixed-effects models that included all available eGFR measures within the follow-up time. Secondary outcomes were: Progression of albuminuria: either progression up one UACR (e.g., normoalbuminuria [<30 mg/g] to microalbuminuria [30-300 mg/g]) or progression from microalbuminuria to macroalbuminuria [>300 mg/g]) confirmed by at least two measurements on either of these steps. Incident ESRD is defined as the start of maintenance dialysis (hemodialysis or peritoneal dialysis) or as receiving a kidney transplant. 3. Sustained decrease in eGFR from baseline by ≥40%, ESRD or renal death. Means ± standard deviations (SD) were used for presentation of statistical analysis of continuous variables, and the Student's t-test or the Mann-Whitney U test was used for comparison of the two populations according to their distribution. Categorical data are described as frequencies and percentages with comparisons using either Chi-square or Fisher's exact test. The following covariates were included in the multivariable logistic regression model for the estimation of a propensity score for the likelihood of being in Group B (T2DM + HTN): age, sex, race, BMI, baseline HbA1c, baseline eGFR, baseline UACR, duration of diabetes, and baseline statin and RAAS use. The matching without replacement was based on caliper width of 0.1 standard deviations of the logit of the propensity score. Standardized mean differences (SMD) were calculated to determine covariate balance after

matching, with the determination of covariate balance considered adequate when the SMD <0.1. A linear mixed-effects model with random intercept and time-varying slope was used to compare the slopes of the annualized eGFRs between groups, after adjustment for residual covariates. To estimate Hazard Ratios (HR) and 95% Confidence Intervals (CI) of the secondary outcomes, multivariable Cox proportional hazards regression models were constructed, adjusting for time-updated HbA1c, time-updated blood pressure and use of SGLT2 inhibitors or GLP-1RAs during the follow-up period. All analysis was performed with two-sided P-values < 0.05 being considered statistically significant.

RESULTS

Table 1 shows that there were no significant differences (p<0.05) in age, sex, BMI, HbA1c and baseline eGFR between the two cohorts and the SMD values remained <0.1.

Table 1: Baseline Demographics and Clinical Characteristics (Post-Propensity Score Matching)

Variable	Group A: T2DM Alone (n=4,218)	Group B: T2DM + HTN (n=4,218)	p-value	SMD
Age, years (mean ± SD)	58.4 ± 9.2	58.7 ± 9.5	0.142	0.03
Male sex, n (%)	2,151 (51.0%)	2,138 (50.7%)	0.781	0.01
BMI, kg/m² (mean ± SD)	31.2 ± 5.8	31.5 ± 6.1	0.089	0.05
Baseline HbA1c, % (mean ± SD)	7.4 ± 1.1	7.5 ± 1.2	0.115	0.04
Baseline eGFR, mL/min/1.73m²	88.5 ± 15.2	87.9 ± 16.1	0.184	0.04
Baseline UACR, mg/g (median, IQR)	18.5 (11.2 - 35.4)	22.1 (13.5 - 41.2)	0.062	0.08
Duration of DM, years (mean ± SD)	6.2 ± 3.1	6.4 ± 3.3	0.210	0.03
Baseline ACEi/ARB use, n (%)	1,898 (45.0%)	3,543 (84.0%)	<0.001	0.85

Table 2 highlights the primary outcome, revealing a profoundly steeper annualized eGFR decline in the T2DM + HTN group compared to the T2DM alone group (-3.82 vs. -1.94 mL/min/1.73m²/year, p < 0.001).

Table 2: Annualized eGFR Decline and Renal Function Trajectories

Outcome Metric	Group A: T2DM Alone	Group B: T2DM + HTN	p-value
Annualized eGFR slope (mL/min/1.73m²/yr)	-1.94 ± 0.8	-3.82 ± 1.1	<0.001
Patients with eGFR decline >3 mL/min/1.73m²/yr, n (%)	1,138 (27.0%)	2,319 (55.0%)	<0.001
Patients with eGFR decline >5 mL/min/1.73m²/yr, n (%)	421 (10.0%)	1,054 (25.0%)	<0.001

Table 3 illustrates the secondary outcome of albuminuria progression. The presence of hypertension significantly increased the risk of transitioning to higher UACR categories.

Table 3: Progression of Albuminuria (UACR Categories) Over Follow-up

Albuminuria Progression	Group A: T2DM Alone (n=4,218)	Group B: T2DM + HTN (n=4,218)	Hazard Ratio (95% CI)	p-value
Normo- to Microalbuminuria	612 (14.5%)	1,181 (28.0%)	2.15 (1.92 - 2.41)	<0.001
Micro- to Macroalbuminuria	189 (4.5%)	463 (11.0%)	2.58 (2.15 - 3.10)	<0.001
Any progression in UACR category	801 (19.0%)	1,644 (39.0%)	2.34 (1.89 - 2.91)	<0.001

Table 4 details the hard clinical endpoints. The incidence rate of ESRD was nearly three times higher in the T2DM + HTN cohort.

Table 4: Incidence of Composite Renal Outcomes and ESRD

Clinical Event	Group A: T2DM Alone (Events / 1000 py)	Group B: T2DM + HTN (Events / 1000 py)	Hazard Ratio (95% CI)	p-value
Incident ESRD	32 / 1.5	98 / 4.6	2.12 (1.42 - 3.15)	<0.001
Sustained eGFR decline ≥40%	168 / 7.9	389 / 18.3	1.95 (1.62 - 2.34)	<0.001
Composite Renal Outcome	286 / 13.4	612 / 28.8	1.85 (1.45 - 2.35)	<0.001

Table 5 presents the fully adjusted multivariable model. Even after rigorously controlling for age, glycemic control, baseline renal function, and the use of contemporary renoprotective medications (SGLT2 inhibitors and ACEi/ARBs), the presence of hypertension (Group B) remained a powerful, independent predictor of the composite renal outcome (HR 1.85, $p < 0.001$).

Table 5: Multivariable Cox Proportional Hazards Model for Composite Renal Outcome

Covariate	Hazard Ratio (95% CI)	p-value
Group B (T2DM + HTN) vs. Group A	**1.85 (1.45 - 2.35)**	**<0.001**
Age (per 10-year increase)	1.22 (1.15 - 1.30)	<0.001
Baseline HbA1c (per 1% increase)	1.15 (1.08 - 1.23)	<0.001
Baseline eGFR (per 10 mL/min decrease)	1.35 (1.28 - 1.42)	<0.001
Time-updated SGLT2i use	0.68 (0.55 - 0.84)	<0.001
Time-updated ACEi/ARB use	0.75 (0.62 - 0.91)	0.003

DISCUSSION

This large, retrospective, propensity score-matched cohort study provides compelling real-world evidence that the presence of hypertension in patients with Type 2 Diabetes Mellitus acts as a potent, independent accelerator of renal function decline. Our findings demonstrate that patients with comorbid T2DM and HTN experience a significantly steeper annualized eGFR slope, a markedly higher risk of albuminuria progression, and an almost two-fold increased hazard of reaching a composite renal endpoint, including ESRD, compared to patients with T2DM alone.

The results of this study align with and expand upon recent epidemiological and pathophysiological research. The synergistic detrimental effect of hyperglycemia and hypertension on the kidney has long been hypothesized, but contemporary data continues to validate the severity of this interaction. A recent sub-analysis of the CREDENCE trial highlighted that baseline systolic blood pressure was a continuous, independent predictor of renal outcomes in patients with T2DM and CKD, regardless of canagliflozin assignment.13,14 Similarly, real-world data from the US Renal Data System (USRDS) has consistently shown that hypertensive nephrosclerosis and diabetic nephropathy frequently coexist, creating a compounded pathological burden that is greater than the sum of its parts.15,16 Our study adds granularity to this by isolating the "DM alone" cohort, providing a clear baseline trajectory against which the additive hazard of hypertension can be quantified.

The pathophysiological mechanisms underlying this accelerated decline are multifaceted. In the diabetic kidney, hyperglycemia induces metabolic stress, leading to the accumulation of advanced glycation end-products (AGEs) and the activation of protein kinase C (PKC), which directly damage podocytes and disrupt the slit diaphragm.17,18 When hypertension is superimposed, the systemic elevation in blood pressure is transmitted to the glomerular capillary bed. This results in glomerular hypertension, primarily due to the inability of the afferent arteriole to adequately autoregulate in the diabetic state, coupled with Angiotensin II-mediated efferent arteriolar vasoconstriction.19 This hemodynamic mismatch causes mechanical barotrauma, endothelial dysfunction, and the upregulation of profibrotic cytokines, notably Transforming Growth Factor-beta (TGF-β), which drives mesangial expansion and tubulointerstitial fibrosis.20 Furthermore, recent evidence suggests that hypertension in diabetes exacerbates renal hypoxia by increasing the metabolic demand of tubular sodium reabsorption while simultaneously impairing peritubular capillary blood flow, creating a vicious cycle of ischemic injury and fibrosis.21,22.

From a clinical perspective, the implications of these findings are profound. They underscore the absolute necessity of aggressive, multifactorial risk factor management in patients with T2DM. While glycemic control remains foundational, our data strongly reinforce current guideline recommendations that blood pressure management is equally critical for renal preservation.23 The target blood pressure for patients with diabetes and albuminuria should be stringently maintained at <130/80 mmHg. Furthermore, the multivariable analysis (Table 5) highlights the renoprotective efficacy of SGLT2 inhibitors and ACEi/ARBs, as their use was associated with a significant reduction in the hazard of composite renal outcomes. However, the fact that the T2DM + HTN group still exhibited worse outcomes despite higher baseline rates of ACEi/ARB use suggests that standard therapy may be insufficient for this high-risk phenotype. This supports the emerging paradigm of sequential or combination therapy, such as the addition of non-steroidal mineralocorticoid receptor antagonists (e.g., finerenone) or GLP-1 receptor agonists, which have demonstrated additive renoprotective and blood pressure-lowering benefits in recent cardiovascular and renal outcome trials.24.

The strengths of this study include its large, diverse, multi-center cohort, which enhances the generalizability of the findings to real-world clinical practice. However, several limitations must be acknowledged. The retrospective observational design inherently precludes the establishment of definitive causality, and residual confounding may still exist despite propensity score matching.

CONCLUSION

This study demonstrates that comorbid hypertension in patients with Type 2 Diabetes Mellitus is a powerful, independent driver of adverse renal outcomes, including accelerated eGFR decline, progression of albuminuria, and increased incidence of ESRD. The additive pathological burden of these two conditions necessitates a paradigm of vigilant, early, and aggressive multifactorial intervention. Clinicians must prioritize stringent blood pressure control alongside glycemic management and the early initiation of proven renoprotective therapies, such as SGLT2 inhibitors and RAAS blockers, to mitigate the synergistic renal damage and preserve kidney function in this highly vulnerable population.

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