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Original Article

Internal Medicine Section

Effect of SGLT2 Inhibitors on Renal Resistive Index in Diabetic Nephropathy Patients: A Quasi-experimental Study

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ABSTRACT

Introduction: Diabetic Nephropathy (DN) is a frequent and severe complication of Type 2 Diabetes Mellitus (T2DM) that often progresses to End-Stage Renal Disease (ESRD). Renal Resistive Index (RI) and Urine Albumin-to-Creatinine Ratio (UACR) are valuable indicators used to evaluate renal microvascular health and DN progression. Doppler ultrasonography of the renal arteries is a non invasive tool for analysing renal blood flow, with RI providing insight into vascular resistance by comparing systolic and diastolic flow velocities.

Aim: To assess the impact of sodium-glucose cotransporter 2 (SGLT2) inhibitors on RI in T2DM patients.

Materials and Methods: A quasi-experimental study involving 148 participants, categorised into normoalbuminuric and microalbuminuric groups, was conducted at SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India. Patients received SGLT2 inhibitors for three months, after which RI and UACR were reassessed. Paired t-tests were used to compare pre- and postintervention values within groups, while independent t-tests and Chi-square tests were applied to compare baseline characteristics and outcomes between groups. A p-value <0.05 was considered statistically significant.

Results: Post-treatment findings showed significant reductions in RI and UACR values, indicating improved renal haemodynamics and reinforcing the renal protective role of SGLT2 inhibitors (p-value <0.001).

Conclusion: These results underscore the therapeutic relevance of SGLT2 inhibitors in preserving renal microcirculation and delaying DN progression.

Keywords: Albuminuria, Diabetic kidney disease, Doppler, Gliflozins, Renal circulation, Ultrasonography

INTRODUCTION

Declining kidney function markedly increases the risk of both renal and cardiovascular complications. An elevated renal RI, defined as a value above 0.7, is a recognised marker of subclinical renal impairment and increased vascular resistance [1,2]. Prior studies suggest that interventions such as renal denervation (RDN) may lower RI, improve renal perfusion, and support functional stability [3,4]. The ESRD represents the final stage of chronic kidney dysfunction, with DN being one of its leading causes globally. Once DN develops, the damage is often irreversible. While tight control of blood glucose and blood pressure reduces the risk of developing Diabetic Kidney Disease (DKD), progression, once established, can only be delayed [5]. SGLT2 inhibitors, a newer class of oral hypoglycaemic agents, have emerged as potential nephroprotective agents due to their glucose-lowering effects and additional benefits, including reductions in blood pressure and improvements in renal function. However, their efficacy in glycaemic control diminishes in patients with impaired renal function, as their action depends on glomerular filtration rate [6].

SGLT2 inhibitors act by blocking glucose reabsorption in the proximal tubules, thereby enhancing urinary glucose excretion and improving blood glucose control. Beyond glycaemic effects, these agents reduce glomerular hyperfiltration and minimise tissue injury, helping to slow the progression of DKD [7]. They are also associated with weight reduction, improved metabolic parameters, and decreased oxidative stress and inflammation, which are key contributors to kidney damage. These pleiotropic effects position SGLT2 inhibitors as a cornerstone in the comprehensive management of diabetes-related kidney disease [8].

Currently, four SGLT2 inhibitors are approved for use in adults: empagliflozin, ertugliflozin, dapagliflozin, and canagliflozin. Their renoprotective properties are now widely recognised, independent of their role in glycaemic regulation. These medications not only reduce systemic blood pressure and albuminuria but also help in preventing further renal deterioration in diabetic patients [8]. Additionally, they assist in addressing metabolic abnormalities such as hyperuricaemia and contribute to cardiovascular protection by promoting ketogenesis, which may serve as an alternative energy source for the heart and enhance its performance [9].

The renal artery RI is a vital diagnostic parameter in ultrasonography that offers insight into renal haemodynamics by measuring resistance to blood flow in the renal arteries. It is derived from two Doppler waveform parameters: Peak Systolic Velocity (PSV) and End-Diastolic Velocity (EDV). PSV reflects the maximum flow rate during cardiac contraction, while EDV represents flow during cardiac relaxation [10]. Though frequently used in nephrology, the renal RI is sometimes misinterpreted. It reflects structural and functional changes in the kidney that influence vascular resistance, thus positioning it as a potential early marker of renal pathology [11]. Emerging evidence from clinical studies [12-16] suggests that SGLT2 inhibitors lower albuminuria, attenuate glomerular hyperfiltration, and reduce renal stress in diabetic patients. Despite these promising findings, the mechanisms underlying these effects remain partially unclear, and much of the existing research focuses on Type 1 Diabetes Mellitus (T1DM) [17]. There is still a need to explore their efficacy in T2DM and non diabetic Chronic Kidney Disease (CKD) populations. Furthermore, these drugs improve vascular elasticity and reduce arterial stiffness by enhancing endothelial function through vasodilation and reduced cellular inflammation. Although albuminuria is a well-established marker of DN, it often manifests only after considerable renal damage has occurred. Emerging evidence suggests that renal RI, assessed through Doppler ultrasonography, may detect early microvascular alterations even in normoalbuminuric

individuals [18]. However, the prognostic significance of elevated RI in this early stage remains inadequately explored. This study was designed to investigate the impact of SGLT2 inhibitors on RI as measured by Doppler ultrasonography.

MATERIALS AND METHODS

This pre-post quasi-experimental study was conducted at SRM Medical College and Hospital, Kattankulathur, Chennai, Tamil Nadu, India from October 2023 to December 2024, to assess the effect of SGLT2 inhibitors on renal RI in patients with DN. The study population included patients with DN, in whom RI was measured at baseline (preintervention) and at specified intervals after initiating SGLT2 inhibitor therapy (postintervention). The same individuals thus served as their own controls. Each participant's data were collected and followed-up for a period of three months. Hence, all participant data were collected from October 2023 and followed up until December 2024 (total duration for recruitment and follow-up). The Institutional Ethics Committee (IEC) approved the study protocol. Ethics clearance number: SRMIEC-ST-0723-773. Written informed consent was obtained from every participant in this investigation.

Inclusion criteria: Participants aged >18 years with a history of T2DM, estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2, and a urine ACR <300 mg/g were eligible [19]. All participants were stably treated with oral antihyperglycaemic drugs other than SGLT2 inhibitors prior to enrolment.

Exclusion criteria: Patients with obstructive uropathy, congenital or acquired renal anomalies, nephrotoxic drug use, refractory hypertension, recent SGLT2 inhibitor or insulin use (within the previous four weeks), severe hepatic insufficiency, dehydration risk (e.g., diuretic use or chronic diarrhoea), recurrent urinary tract infection, active infection or fever, peripheral vascular disease, and menstruating women were excluded from the study.

Sample size: Based on Krishnan V et al., [20], the sample size was calculated using the following equation:

$$n = \frac{\{(Z\alpha/2+Z1-\beta)^2 \times (P1Q1+P2Q2)\}}{(P1-P2)^2}$$

Where n = required sample size per group; $Z\alpha/2$ = standard normal deviate for two-tailed alpha (e.g., 1.96 for 5% level of significance); $Z1-\beta$ = standard normal deviate for power (e.g., 0.84 for 80% power); P1, P2 = expected proportions in each group; where P1 = 0.96; P2 = 0.82; Q1 = 1 – P1 = 0.04, Q2 = 1 – P2 = 0.18, P1 - P2 = 0.14 which is the effect size.

Sensitivity: 81.7 %

Specificity: 96.3 %

The expected value for sensitivity and specificity was derived from a previous study [19] conducted in a comparable population, and hence was adopted for the current analysis.

Level of significance: 5% Power of study: 80%

Sample size=$\{(Z\alpha/2+Z1-\beta)^2 * (P1Q1+P2Q2)\}/(P1-P2)^2$

=$\{(1.96+0.84)^2 * (0.96*0.04+0.82*0.18)\}/(0.96-0.82)^2$

=$\{(2.8)^2 * (0.0384+0.1476)\}/(0.14)^2$

=(7.84 * 0.1860) / 0.0196

=1.45824/0.0196

=74

In this study, two distinct sets of sample groups were employed. Specifically, Group I (n1) consisted of 73 normoalbuminuric participants, while Group II (n2) consisted of 75 microalbuminuric participants to evaluate the impact of SGLT2 inhibitors across different stages of DN. This stratification is clinically significant, as albuminuria levels serve as early markers of glomerular damage and renal disease progression. Normoalbuminuria represents an early-stage nephropathy, often reversible with timely intervention, while microalbuminuria reflects the onset of structural renal damage [21].

The study employed convenient sampling, enrolling participants based on availability and fulfillment of inclusion criteria, resulting in 73 participants in n1 and 75 in n2, within which participants in n2 were further sub grouped according to their microalbuminuria level. Although the calculated sample size was 74 per group (total 148), this minor deviation occurred due to practical constraints such as participant availability, willingness, and occasional dropouts. Importantly, the total sample size and statistical power were preserved, and analyses were conducted accordingly. While nonprobabilistic, convenient sampling was a practical choice in this quasi-experimental clinical setting, allowing timely recruitment and inclusion of real-world patients, thereby enhancing the relevance and applicability of the findings.

Categorisation of study population according to urine ACR levels: Participants were classified based on urinary ACR into:

- **Group 1:** 73 participants- Normoalbuminuria (ACR < 30 mg/g)
- **Group 2:** 22 participants- Microalbuminuria (ACR 30–100 mg/g)
- **Group 3:** 15 participants- ACR 101–200 mg/g
- **Group 4:** 38 participants- ACR 201–300 mg/g

This subcategorisation [22] enabled assessment of the renal RI response to SGLT2 inhibitor therapy across varying degrees of albuminuria. All patients received SGLT2 inhibitors as part of their DN treatment. All participants received dapagliflozin 10 mg once daily as the standardised SGLT2 inhibitor throughout the study period. RI was measured at baseline and after three months of therapy. Baseline characteristics, including age, gender, duration of diabetes, and co-morbidities, were recorded.

Ultrasound protocol:

Renal Resistive Index (RI) Measurement protocol

RI was measured using a standardised Doppler ultrasound protocol. Patients were examined in a fasting state, positioned supine or in a slight lateral decubitus position to minimise bowel gas interference. A 3–5 MHz convex transducer was employed with an insonation angle ≤60°, low wall filter settings, and optimised gain to accurately capture low diastolic flow.

RI was assessed in the segmental or interlobar (intrarenal) arteries of both kidneys. Using a longitudinal view of the kidneys, colour Doppler imaging was applied to localise the target arteries. PSV and EDV were recorded, and the RI was calculated using the formula:

RI= (PSV-EDV)/PSV [23].

Three measurements were obtained from each kidney, and the mean value was used for analysis. Care was taken to apply minimal probe pressure to avoid artificially elevated diastolic velocity measurements. Renal artery Doppler assessments were independently performed by two radiologists who were blinded to the study objectives. Standardised protocols were uniformly followed, including identical sampling sites, the number of measurements per kidney, and preset Doppler parameters (low wall filter and Doppler angle ≤60°). This approach was employed to minimise interobserver variability.

Laboratory measurements: Serum creatinine, haemoglobin A1c (HbA1c), and urine albumin-to-creatinine ratio (ACR) were estimated.

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 20.0. Continuous variables were presented as mean±standard deviation (SD). The categorical variables were examined with the Chi-square test. A p-value <0.05 was considered statistically significant. Normality of continuous

variables was assessed using the Shapiro-Wilk test. Since the data followed a normal distribution, results were expressed as mean±SD. Confidence intervals and p-values have been reported for all relevant statistical comparisons.

RESULTS

Urine ACR categories distribution by age, gender, and age-based correlation: Lower ACR levels (Group 1: 0-29 mg/g) were common in ages 41-60, while higher levels (Group 4: 201-300 mg/g) predominated in ages 61-70, though the age-ACR association was not significant (p-value=0.0980). Females were more frequent in lower ACR groups, and males in higher ones, with a significant gender-ACR association (p-value=0.0011). No significant association was found between the prevalence of hypertension and dyslipidaemia and the different ACR groups [Table/Fig-1].

Correlation of urine ACR groups and serum creatinine concentrations: The [Table/Fig-2] describes the serum creatinine distribution within the four groups of urine ACR. A significant association was found between serum creatinine and urine ACR category (p-value <0.001).

Association of urine ACR classes and Glycated Haemoglobin (HbA1c): The majority of patients across all urine ACR categories had HbA1c values between 5.0-10.0%, amounting to 135 (91.2%), with only a small percentage, i.e., 12 (8.1%), exceeding 10.0%, indicating poor glycaemic control. The distribution was similar across all groups, with no significant association between HbA1c levels and urine ACR category (p-value=0.8466), suggesting that glycaemic control did not significantly differ between albuminuria groups [Table/Fig-3].

Distribution of urine ACR and bilateral renal Resistive Index (RI): Right kidney RI increased from 0.73 in Group 1 to 0.867 in Group 4, with 7 (8.4%) participants in Group 4 having RI > 0.9. The association of RI with ACR was significant (p-value <0.001) [Table/Fig-4]. Left kidney RI showed a similar rise (0.73 to 0.86), with 4 (10.5%) participants in Group 4 having RI >0.9. The association of RI with ACR was also significant (p-value <0.001) [Table/Fig-5].

In Group 1, among subjects with RI values between 0.7 and 0.9 for both kidneys, the right kidney RI showed a moderate and statistically significant positive correlation with ACR (r-value=0.48, p-value <0.0001), while the left kidney correlation was weak (r-value=0.07, p-value=0.569). However, both kidneys demonstrated a positive trend, suggesting early vascular changes associated with increasing albuminuria.

Distribution of urine ACR and bilateral renal Resistive Index (RI) after three months of SGLT2 inhibitor therapy: After three months, 137 (92.6%) had right kidney RI <0.7, with a significant association between ACR and RI (p-value=0.02) [Table/Fig-6]. The mean RI decreased across all groups, with Group 1 at 0.60 and Group 4 at 0.63. The maximum RI dropped from 1.00 to 0.74, indicating improved renal vascular resistance. Group 4's median RI also fell from 0.85 to 0.61, highlighting the beneficial impact of SGLT2 inhibitors on renal function [Table/Fig-7].

Variables	Group 1 (ACR <30 mg/g)	Group 2 (ACR 30-100 mg/g)	Group 3 (ACR 101-200 mg/g)	Group 4 (ACR 201-300 mg/g)	Total (n=148)	p-value
Age (mean±SD)	51.1±10.3	56.1±8.9	42.7±12.1	52.1±9.7	50.8±10.2	0.098
Gender (M/F)	28/45	5/17	13/2	16/22	62/86	0.0011
Duration of diabetes (years)	6.5±2.3	7.8±2.0	5.2±2.6	8.0±1.9	6.9±2.3	<0.01
Hypertension (%)	34 (46.57%)	22 (100%)	10 (66.66%)	15 (39.47%)	81 (54.72%)	0.80
Dyslipidemia (%)	28 (38.35%)	20 (9.09%)	9 (60%)	13 (34.21%)	70 (47.29%)	0.88

[Table/Fig-1]: Baseline characteristics of study participants.

Urine ACR category S. Creatine	Group 1 N (%)	Group 2 N (%)	Group 3 N (%)	Group 4 N (%)	Total N (%)	Chi-square test	p-value
0.0-0.5	5 (6.8%)	2 (9.1%)	0	0	7 (4.7%)	51.1312	<0.001
0.6-1.0	58 (79.5%)	20 (90.9%)	12 (80.0%)	14 (36.8%)	104 (70.3%)		
1.1-1.5	10 (13.7%)	0	3 (20.0%)	16 (42.1%)	29 (19.6%)		
Above 1.5	0	0	0	8 (21.1%)	8 (5.4%)		
Mean±SD	0.79±0.21	0.69±0.10	0.99±0.12	1.18±0.40	0.90±0.31		
Total	73 (100.0%)	22 (100.0%)	15 (100.0%)	38 (100.0%)	148 (100.0%)		

[Table/Fig-2]: S. Creatinine distribution by urine ACR category.

Urine ACR category HbA1c	Group 1 N (%)	Group 2 N (%)	Group 3 N (%)	Group 4 N (%)	Total N (%)	Chi-square test	p-value
Less than 5.0	1 (1.4%)	0	0	0	1 (0.7%)	2.6899	0.8466
5.0%-10.0	66 (90.4%)	20 (90.9%)	15 (100.0%)	34 (89.5%)	135 (91.2%)		
More than 10	6 (8.2%)	2 (9.1%)	0	4 (10.5%)	12 (8.1%)		
Total	73 (100.0%)	22 (100.0%)	15 (100.0%)	38 (100.0%)	148 (100.0%)		

[Table/Fig-3]: HbA1c distribution by urine ACR category.

Urine ACR category Resistive Index (RI)	Group 1 N (%)	Group 2 N (%)	Group 3 N (%)	Group 4 N (%)	Total N (%)	Chi-square test	p-value
Less than 0.7	2 (2.7%)	3 (13.6%)	0	0	5 (3.4%)	29.8434	<0.001
0.7-0.9	71 (97.3%)	19 (86.4%)	15 (100.0%)	31 (81.6%)	136 (91.9%)		
More than 0.9	0	0	0	7 (8.4%)	7 (4.7%)		
Mean±SD	0.73±0.01	0.75±0.06	0.78±0.02	0.86±0.07	0.78±0.05		
Total	73 (100.0%)	22 (100.0%)	15 (100.0%)	38 (100.0%)	148 (100.0%)		

[Table/Fig-4]: Resistive Index (RI) distribution by urine ACR Category (Right kidney).

Urine ACR category Resistive Index (RI)	Group 1 N (%)	Group 2 N (%)	Group 3 N (%)	Group 4 N (%)	Total N (%)	Chi-square test	p-value
Less than 0.7	2 (2.7%)	4 (18.2%)	0	0	6 (4.0%)	25.5510	<0.001
0.7-0.9	70 (95.9%)	14 (63.6%)	15 (100.0%)	34 (89.5%)	133 (89.9%)		
More than 0.9	1 (1.4%)	4 (18.2%)	0	4 (10.5%)	9 (6.1%)		
Mean±SD	0.73±0.04	0.78±0.09	0.78±0.02	0.86±0.06	0.79±0.06		
Total	73 (100.0%)	22 (100.0%)	15 (100.0%)	38 (100.0%)	148 (100.0%)		

[Table/Fig-5]: Resistive Index (RI) distribution by urine ACR Category (Left kidney).

Urine ACR category Resistive Index (RI) after 3 months	Group 1 N (%)	Group 2 N (%)	Group 3 N (%)	Group 4 N (%)	Total N (%)	Chi-square test	p-value
Less than 0.7	67 (91.8%)	22 (100.0%)	13 (86.7%)	35 (92.1%)	137 (92.6%)	5.10	0.02
0.7-0.9	6 (8.2%)	0	2 (13.3%)	3 (7.9%)	11 (7.4%)		
More than 0.9	0	0	0	0	0		
Total	73 (100.0%)	22 (100.0%)	15 (100.0%)	38 (100.0%)	148 (100.0%)		

[Table/Fig-6]: Resistive Index (RI) distribution by urine ACR category after 3 months (Right kidney).

ACR group	Resistive Index (RI) mean±SD	Resistive Index (RI) median	Resistive Index (RI) max	Resistive Index (RI) after 3 months of SGLT2 inhibitors mean±SD	Resistive Index (RI) after 3 months of SGLT2 inhibitors median	Resistive Index (RI) after 3 months of SGLT2 Inhibitors max
Group-1 (0-29 mg/g)	0.73±0.01	0.72	0.86	0.60±0.05	0.6	0.78
Group-2 (30-100 mg/g)	0.75±0.06	0.74	0.92	0.60±0.06	0.64	0.68
Group-3 (101-200 mg/g)	0.78±0.02	0.78	0.8	0.63±0.09	0.59	0.68
Group-4 (201-300 mg/g)	0.86±0.07	0.85	1.0	0.63±0.08	0.61	0.74

[Table/Fig-7]: Resistive Index (RI) before and after treatment across ACR groups (Right Kidney).

Similarly, after three months, 130 (87.8%) participants had left kidney RI <0.7, with Group 3 achieving full normalisation. However, 9 (23.7%) participants in Group 4 remained in the 0.7–0.9 range, indicating persistent vascular resistance [Table/Fig-8]. The Chi-square test (p-value=0.024) showed a significant association. The mean left kidney RI decreased acros s all groups, with Group 3 showing the lowest post-treatment value (0.60). Group 4's median RI dropped from 0.85 to 0.63, and the maximum RI reduced from 1.00 to 0.78, reflecting significant reductions in renal vascular resistance after SGLT2 inhibitor therapy [Table/Fig-9].

DISCUSSION

The present study found that treatment with SGLT2 inhibitors significantly reduced renal RI values across all stages of albuminuria in patients with DN, indicating improved renal vascular resistance. The most pronounced decline was observed in Group 4 (ACR 201–300 mg/g), where the median RI fell from 0.85 to 0.61 and the maximum RI fell from 1.00 to 0.74, suggesting meaningful vascular improvement following therapy. In Group 1 (ACR 0–29 mg/g), both the right and left renal RI demonstrated positive associations with urine ACR levels. These findings underscore the potential utility of RI as an early, non invasive marker for monitoring subclinical renal

Urine ACR category Resistive Index (RI) after 3 months	Group 1 N (%)	Group 2 N (%)	Group 3 N (%)	Group 4 N (%)	Total N (%)	Chi-square test	p-value
Less than 0.7	68 (93.2%)	18 (81.8%)	15 (100.0%)	29 (76.3%)	130 (87.8%)	10.9766	0.024
0.7 - 0.9	4 (5.5%)	4 (18.2%)	0	9 (23.7%)	17 (11.5%)		
More than 0.9	1 (1.4%)	0	0	0	1 (0.7%)		
Total	73 (100.0%)	22 (100.0%)	15 (100.0%)	38 (100.0%)	148 (100.0%)		

[Table/Fig-8]: Resistive Index (RI) distribution by urine ACR category after 3 months (Left kidney).

ACR group	Resistive Index (RI) mean±SD	Resistive Index (RI) median	Resistive Index (RI) max	Resistive Index (RI) after 3 months of SGLT2 inhibitors mean±SD	Resistive Index (RI) after 3 months of SGLT2 inhibitors median	Resistive Index (RI) after 3 months of SGLT2 inhibitors max
Group 1 (0-29 mg/g)	0.73±0.04	0.73	1.0	0.61±0.08	0.6	0.93
Group 2 (30-100 mg/g)	0.78±0.09	0.75	0.98	0.63±0.07	0.62	0.73
Group 3 (101-200 mg/g)	0.78±0.02	0.78	0.81	0.60±0.03	0.59	0.64
Group 4 (201-300 mg/g)	0.86±0.06	0.85	1.0	0.64±0.07	0.63	0.78

[Table/Fig-9]: Resistive Index (RI) before and after treatment across ACR groups (Left Kidney).

The intervention led to a significant improvement in both renal RI and urine ACR across all groups (p-value <0.001). Higher baseline ACR groups demonstrated elevated RI initially, but all groups showed marked postintervention reductions, with the greatest improvements seen in Group 4. This consistent decline indicates that the intervention effectively improved renal haemodynamics and reduced albuminuria, with greater absolute benefit observed in patients with higher baseline abnormalities. This is shown in [Table/Fig-10,11], respectively.

vascular changes and assessing response to treatment in DN [3,24,25].

A significant association was observed between gender and ACR levels, with male patients more likely to present with moderate to severe albuminuria. This aligns with the suggestion by Hwang S et al., of an age-related gradient, with older patients exhibiting more severe albuminuria, especially in Group 4, which supports the hypothesis that ageing contributes to renal microvascular damage, either independently or through its interaction with longstanding

ACR group	Preintervention RRI (Mean±SD)	Postintervention RRI (Mean±SD)	p-value
Group 1 (0-29 mg/g)	0.73±0.02	0.6±0.05	<0.001
Group 2 (30-100 mg/g)	0.76±0.08	0.62±0.05	<0.001
Group 3 (101-200 mg/g)	0.78±0.01	0.61±0.05	<0.001
Group 4 (201-300 mg/g)	0.86±0.06	0.63±0.07	<0.001

[Table/Fig-10]: Pre- and postintervention RI (Mean±SD) with p-values.

ACR group	Preintervention urine ACR (Mean±SD)	Postintervention urine ACR (Mean±SD)	p-value
Group 1 (0-29 mg/g)	14.66±7.49	7.62±4.01	<0.001
Group 2 (30-100 mg/g)	53.70±24.33	27.29±19.37	<0.001
Group 3 (101-200 mg/g)	144.73±14.80	73.53±10.49	<0.001
Group 4 (201-300 mg/g)	265.18±33.20	156.66±40.46	<0.001

[Table/Fig-11]: Pre- and postintervention urine ACR (Mean±SD) with p-values.

diabetes [26]. Similarly, this concurs with earlier findings that male gender is an independent risk factor for progressive DKD [27].

Creatinine levels increased with albuminuria severity, supporting the use of ACR as a surrogate marker for progressive renal impairment. In Group 4, a substantial number of participants had creatinine levels >1.5 mg/dL, and this association was statistically significant. The finding that patients in Group 1 (ACR <30 mg/g) had elevated baseline RI suggests the presence of microvascular damage preceding overt albuminuria, which is a crucial insight for early diagnosis and intervention [27].

Importantly, the reduction in RI after three months of SGLT2 inhibitor therapy was significant across all groups, including those with normoalbuminuria and microalbuminuria. This reinforces emerging evidence that the renal benefits of SGLT2 inhibitors extend beyond glycemic control and include haemodynamic and endothelial mechanisms. The lack of a significant association between HbA1c and ACR further supports this dissociation [28]. The findings are consistent with previous studies. Solini A et al., demonstrated that even a short-term course of dapagliflozin significantly improved RI in patients with T2DM, likely via reductions in oxidative stress [29]. Aroor AR et al., reported similar benefits with empagliflozin, including reductions in RI, arterial stiffness, and tubular injury markers over five weeks [30]. These results resonate with the present study, which showed consistent RI improvement over a longer three-month period.

Furthermore, landmark clinical trials such as EMPA-REG OUTCOME, DAPA-CKD, and CANVAS have established the role of SGLT2 inhibitors in reducing albuminuria and preserving eGFR in patients with diabetes [12-14]. However, this study adds to this body of evidence by highlighting RI as a sensitive imaging biomarker that can detect vascular changes even in patients without significant albuminuria. This has implications for expanding the criteria for early initiation of SGLT2 inhibitors in high-risk diabetic patients, even before classical signs of nephropathy emerge.

Mechanistically, the improvement in RI aligns with the known actions of SGLT2 inhibitors: reduction in intraglomerular pressure via afferent vasoconstriction, restoration of tubuloglomerular feedback, and downstream anti-inflammatory and antifibrotic effects [20]. These mechanisms help preserve microvascular integrity and delay the structural progression of nephropathy.

This study affirms that SGLT2 inhibitors significantly improve renal vascular health, as reflected by reduced RI and ACR values. The use of RI provides an additional layer of early detection, particularly in normoalbuminuric individuals, and supports earlier initiation of renoprotective therapies in diabetes management.

Limitation(s)

This study has several limitations. First, the short follow-up period of three months restricts conclusions about the durability of observed effects. Second, only a fixed dose of dapagliflozin was administered, precluding dose–response assessment. Third, although the pre-post design allows within-subject comparison, it cannot fully account for temporal confounding. Treatment adherence was assessed via pill counts and follow-up visits, but detailed adherence tracking and adverse event monitoring were not systematically undertaken. Additionally, potential confounders, such as dietary intake, physical activity, and concurrent use of nephroprotective agents such as Angiotensin-Converting-Enzyme (ACE) inhibitors or Angiotensin-II Receptor Blockers (ARBs), were not adjusted for in the analysis. Finally, the use of convenience sampling from a single tertiary care centre may limit the external validity of the findings. Future studies with randomised controlled designs, longer follow-up durations, and multicentre enrolment are needed to substantiate and generalise these results.

CONCLUSION(S)

This quasi-experimental study highlights the positive impact of SGLT2 inhibitors on renal vascular resistance in patients with DN. A significant reduction in renal RI was observed in both kidneys after three months of treatment, particularly among individuals with more severe albuminuria. These findings suggest that RI can serve not only as a diagnostic marker but also as a useful parameter for tracking treatment effectiveness in DKD. Elevated RI values in normoalbuminuric patients were indicative of early renal microvascular alterations, suggesting that vascular injury may precede detectable albuminuria. This reinforces the potential of RI as an early predictor of nephropathy, allowing for timely intervention before more advanced damage occurs. Despite similar levels of glycaemic control across patient groups, the improvements in RI and albuminuria were notable. This suggests that the benefits of SGLT2 inhibitors on renal health may extend beyond their glucose-lowering effects and involve direct haemodynamic and vascular protective mechanisms.

In conclusion, SGLT2 inhibitors show promise as an effective treatment option in DN, contributing to the preservation of kidney function by improving microvascular dynamics and reducing albuminuria. These findings support their use in the early and ongoing management of patients with T2DM at risk for renal complications.

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REFERENCES

[1] Provenzano M, Rivoli L, Garofalo C, Faga T, Pelagi E, Perticone M, et al. Renal resistive index in chronic kidney disease patients: Possible determinants and risk profile. PLoS One. 2020;15(4):e0230020.
[2] Viazzi F, Leoncini G, Derchi LE, Pontremoli R. Ultrasound doppler renal resistive index- A useful tool for the management of the hypertensive patient. J Hypertens. 2014;32(1):149-53.
[3] Manukyan M, Falkovskaya A, Mordovin V, Pekarskiy S, Zyubanova I, Solonskaya E, et al. Favorable effect of renal denervation on elevated renal vascular resistance in patients with resistant hypertension and type 2 diabetes mellitus. Front Cardiovasc Med. 2022;9:1010546.
[4] Wallbach M, Ajrab J, Bayram B, Pieper D, Schäfer AK, Lüders S, et al. Effects of SGLT2 inhibitors on parameters of renal venous congestion in intrarenal Doppler ultrasonography. Clin Kidney J. 2024;17(9):sfae234.
[5] Sagoo MK, Gnudi L. Diabetic nephropathy: An overview. In: Diabetic nephropathy: Methods Mol Biol. 2020;2067:3-7.
[6] Girardi AC, Polidoro JZ, Castro PC, Pio-Abreu A, Noronha IL, Drager LF. Mechanisms of heart failure and chronic kidney disease protection by SGLT2 inhibitors in nondiabetic conditions. Am J Physiol Cell Physiol. 2024;327(3):C525-C544.
[7] Hasan I, Rashid T, Jaikaransingh V, Heilig C, Abdel-Rahman EM, Awad AS. SGLT2 inhibitors: Beyond glycemic control. J Clin Transl Endocrinol. 2024;2024:100335.
[8] Dronavalli S, Duka I, Bakris GL. The pathogenesis of diabetic nephropathy. Nat Clin Pract Endocrinol Metab. 2008;4(8):444-52.
[9] Umanath K, Lewis JB. Update on diabetic nephropathy: Core curriculum 2018. Am J Kidney Dis. 2018;71(6):884-95.

[10] Zhu H, Chen Y, Ding D, Chen H. Association between different insulin resistance indices and all-cause mortality in patients with diabetic kidney disease: A prospective cohort study. Front Endocrinol. 2025;15:1427727.
[11] Usman MS, Bhatt DL, Hameed I, Anker SD, Cheng AYY, Hernandez AF, et al. Effect of SGLT2 inhibitors on heart failure outcomes and cardiovascular death across the cardiometabolic disease spectrum: A systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2024;12(7):447-61.
[12] Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436-46.
[13] Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375(4):323-34.
[14] Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644-57.
[15] Vallon V. Mechanisms of action of SGLT2 inhibitors and clinical implications. Am J Hypertens. 2024;37(11):841-52.
[16] Cherney DZI, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation. 2014;129(5):587-97.
[17] Apperloo EM, et al. Efficacy and safety of SGLT2 inhibitors with and without glucagon-like peptide 1 receptor agonists: A SMART-C collaborative meta-analysis of randomised controlled trials. Lancet Diabetes Endocrinol. 2024;12(8):545-57.
[18] Bruno RM, Daghini E, Landini L, Versari D, Salvati A, Santini E, et al. Dynamic evaluation of renal resistive index in normoalbuminuric patients with newly diagnosed hypertension or type 2 diabetes. Diabetologia. 2011;54(9):2430-39.
[19] Nishiyama A, Kitada K. Possible renoprotective mechanisms of SGLT2 inhibitors. Front Med (Lausanne). 2023;10:1115413. Doi: 10.3389/fmed.2023.1115413. PMID:36968844; PMCID:PMC10033659.
[20] Krishnan V, Malik A. Role of intrarenal resistive index and ElastPQ® renal shear modulus in early diagnosis and follow-up of diabetic nephropathy: A prospective study. Ultrasound. 2020;28(4):246-54. Doi: 10.1177/1742271X20942249. Epub 2020 Jul 14. PMID: 36959891; PMCID: PMC10028382.
[21] Sánchez-Rodríguez E, Rodríguez-González A, Fernández-Fernández B, Olivares J, Egido J, Ortiz A. Early renal and vascular damage within the normoalbuminuria condition. J Hypertens. 2021;39(11):2220-31.
[22] KDOQI. KDOQI Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis. 2007;49(2 Suppl 2):S12-154. doi: 10.1053/j.ajkd.2006.12.005. PMID: 17276798.
[23] Platt JF, Rubin JM, Ellis JH, DiPietro MA. Duplex Doppler US of the kidney: Differentiation of obstructive from nonobstructive dilatation. Radiology. 1989;171(2):515-17. Doi: 10.1148/radiology.171.2.2649925. PMID: 2649925.
[24] Lytvyn Y, Kimura K, Peter N, Lai V, Tse J, Cham L, et al. Renal and vascular effects of combined SGLT2 and angiotensin-converting enzyme inhibition. Circulation. 2022;146(6):450-62.
[25] Kawanami D, Matoba K, Takeda Y, Nagai Y, Akamine T, Yokota T, et al. SGLT2 inhibitors as a therapeutic option for diabetic nephropathy. Int J Mol Sci. 2017;18(5):1083.
[26] Hwang S, Lee K, Park J, Kim DH, Jeon J, Jang HR, et al. Prognostic significance of albuminuria in elderly of various ages with diabetes. Sci Rep. 2023;13(1):7079. Doi: 10.1038/s41598-023-32305-0. PMID: 37127663; PMCID: PMC10151322.
[27] Gigante A, Pellicano C, De Marco O, Assanto E, Sorato G, Palladini A, et al. Changes in renal microcirculation in patients with nephrotic and nephritic syndrome: The role of resistive index. Microvasc Res. 2024;152:104641.
[28] Aroor AR, Das NA, Carpenter AJ, Nistala R, Bhandari B, Hayden MR, et al. Glycemic control by the SGLT2 inhibitor empagliflozin decreases aortic stiffness, renal resistivity index and kidney injury. Cardiovasc Diabetol. 2018;17:108. Doi: 10.1186/s12933-018-0750-8.
[29] Solini A, Giannini L, Seghieri M, Vitolo E, Taddei S, Ghiadoni L, et al. Dapagliflozin acutely improves endothelial dysfunction, reduces aortic stiffness and renal resistive index in type 2 diabetic patients: A pilot study. Cardiovasc Diabetol. 2017;16:138. Doi: 10.1186/s12933-017-0621-2.
[30] Aroor AR, Whaley-Connell A, Sowers JR. Renal resistive index as a novel biomarker for cardiovascular and kidney risk reduction in type II diabetes. J Clin Hypertens (Greenwich). 2020;22(2):231.

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