E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.48047/ijprt/15.02.111

Effect of Angiotensin Receptor Blockers on Renal Function Biomarkers in Early-Stage Diabetic Nephropathy

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Abstract

Angiotensin receptor blockers (ARBs) are established agents in slowing diabetic nephropathy progression; however, their impact on emerging biomarkers in early-stage disease remains under-explored. In this randomized experimental trial, 140 type 2 diabetic patients with microalbuminuria (30–300 mg/day), preserved estimated glomerular filtration rate (eGFR ≥60 mL/min/1.73 m²), and no prior ARB therapy were randomized to receive losartan (50 mg daily) or placebo over six months. Primary outcomes included changes in urinary neutrophil gelatinase-associated lipocalin (uNGAL), serum cystatin C, and urinary albumin-to-creatinine ratio (UACR). At six months, the losartan group demonstrated a significant reduction in UACR (from 192 ± 45 to 128 ± 38 mg/g; $p < 0.001$), uNGAL (from 45 ± 12 to 31 ± 10 ng/mL; $p < 0.001$), and serum cystatin C (from 0.98 ± 0.12 to 0.91 ± 0.11 mg/L; $p = 0.02$), whereas placebo-treated subjects showed no significant changes. Between-group differences remained significant ($p < 0.001$ for UACR and uNGAL; $p = 0.03$ for cystatin C). ARB therapy was well tolerated, with no serious adverse events. These results suggest that losartan attenuates early tubular and glomerular injury markers beyond albuminuria in early diabetic nephropathy, indicating renoprotective mechanisms that warrant consideration in early intervention strategies. Future studies should investigate the long-term prognostic value of these biomarker improvements.

Keywords: angiotensin receptor blockers; diabetic nephropathy; renal biomarkers.

Introduction

Diabetic nephropathy (DN) remains the leading cause of chronic kidney disease (CKD)

worldwide, with early identification and intervention being critical to preventing progression to end-stage renal disease (2022). While albuminuria serves as the traditional marker for early kidney damage, its sensitivity is limited, particularly in detecting tubular injury. Emerging biomarkers such as urinary neutrophil gelatinase-associated lipocalin (uNGAL) and serum cystatin C provide enhanced sensitivity for glomerular and tubular dysfunction and may better reflect early pathophysiological changes.1-4

Angiotensin receptor blockers (ARBs) have consistently demonstrated efficacy in reducing albuminuria and slowing GFR decline in type 2 diabetes; however, evidence regarding their effects on non-albuminuric injury markers is limited. A 2022 meta-analysis indicated that ARBs may reduce urinary biomarkers of tubular injury, yet most included studies enrolled participants with established nephropathy, limiting conclusions about early-stage effects (2022). For intervention to be most effective, evaluation during early DN—when microalbuminuria is present but eGFR remains near-normal—is essential.5-7

uNGAL, secreted from damaged tubular epithelial cells, has been shown to rise before creatinine or albuminuria elevations in diabetic populations. Similarly, serum cystatin C, a marker of GFR independent of muscle mass, detects subtle reductions in filtration earlier than creatinine-based estimates. Thus, assessing the impact of ARBs on these biomarkers could elucidate mechanisms that precede overt albuminuria reduction.8-10

The present experimental trial investigates whether losartan administered at standard doses over six months alters uNGAL, cystatin C, and UACR levels in patients with early-stage DN. It is hypothesized that ARB therapy will significantly reduce all three markers, reflecting comprehensive nephron protection. The study aims to close knowledge gaps in early intervention effects and inform future biomarker-driven therapeutic strategies.

Methodology

A randomized, double-blind, placebo-controlled design was conducted in patients with type 2 diabetes at University of health sciences. Eligibility criteria included age 40–70 years, microalbuminuria (UACR 30–300 mg/g on two occasions), eGFR ≥60 mL/min/1.73 m² by CKD-EPI, stable glycemic control (HbA1c ≤8%), and no prior ARB or ACE inhibitor use in past six months. Exclusion criteria encompassed macroalbuminuria, uncontrolled hypertension (BP ≥160/100 mmHg), non-diabetic renal disease, use of NSAIDs, active infection or inflammation,

and hepatic dysfunction. Ethics approval was obtained, and verbal informed consent documented in case report forms.

Sample size estimation using Epi Info v7.2 targeted detection of a 20% relative change in uNGAL, anticipated SD of 25%, α=0.05, power 80%. Required sample per arm was calculated as 60; allowing for 15% attrition, total enrollment of 140 patients (70 per group) was achieved. Following baseline assessment—including demographics, blood pressure, glycemic profile, UACR, uNGAL (measured by immunoassay), cystatin C (immunoturbidimetric), serum creatinine, and eGFR—subjects were randomized to losartan 50 mg once daily or matching placebo for six months.

Fasting morning spot urine for UACR and uNGAL, and serum cystatin C assessments were repeated at three and six months. Blood pressure was monitored monthly, and adherence assessed via pill counts. Adverse events were recorded. Laboratory assays followed standardized methods, and inter-assay coefficients of variation, maintained below 5%, ensured assay reliability.

Statistical analysis employed SPSS v28. Normality was evaluated via Shapiro–Wilk test. Continuous variables are expressed as mean ± SD; categorical variables as number (percentage). Between-group comparisons used independent t-tests or Mann–Whitney U as appropriate; within-group changes analyzed by paired t-tests. Repeated-measures ANOVA assessed trends over time. All tests were two-tailed with significance set at $p < 0.05$.

Results

Table 1. Baseline demographic and renal function characteristics

Parameter	**Losartan (n=70)**	**Placebo (n=70)**	**p-value**
Age (years)	56.8 ± 7.4	57.3 ± 7.2	0.67
Male, n (%)	38 (54%)	36 (51%)	0.71
HbA1c (%)	7.2 ± 0.5	7.1 ± 0.6	0.38
Systolic BP (mmHg)	132 ± 9	130 ± 8	0.12
eGFR (mL/min/1.73 m²)	81.5 ± 10.2	82.1 ± 9.8	0.68
UACR (mg/g)	195 ± 53	192 ± 50	0.78

Table 2. Changes in renal biomarkers at six months

Biomarker	Losartan Baseline → 6 mo	Placebo Baseline → 6 mo	Between-Group p-value
UACR (mg/g)	192 ± 45 → 128 ± 38	190 ± 50 → 182 ± 47	<0.001
uNGAL (ng/mL)	45 ± 12 → 31 ± 10	44 ± 13 → 42 ± 12	<0.001
Cystatin C (mg/L)	0.98 ± 0.12 → 0.91 ± 0.11	0.97 ± 0.11 → 0.96 ± 0.12	0.03

Table 3. Repeated measures ANOVA trends over time

Biomarker	Group	Time Effect p-value	Group×Time Interaction p-value
UACR	Losartan	<0.001	<0.001
	Placebo	0.12	
uNGAL	Losartan	<0.001	<0.001
	Placebo	0.48	
Cystatin C	Losartan	0.04	0.02
	Placebo	0.76	

Baseline characteristics were comparable. Losartan significantly reduced UACR, uNGAL, and cystatin C at six months, with robust group-by-time interactions supporting treatment effect.

Discussion

Losartan administration for six months in early diabetic nephropathy significantly attenuated both tubular (uNGAL) and glomerular (UACR, cystatin C) biomarkers, demonstrating renoprotective effects beyond standard albuminuria reduction. This aligns with recent evidence that ARBs preserve tubular integrity, as seen in similar cohorts. The observed decrease in uNGAL reinforces the hypothesis that early ARB therapy mitigates subclinical tubular injury, which might otherwise progress silently.11-13

Reductions in serum cystatin C, albeit modest, represent meaningful improvement in GFR-sensitive markers and contrast with studies indicating stable filtration in placebo groups.14-15 These results support the premise that ARB therapy benefits extend to microfiltration regulation. The early-stage intervention window appears critical for realizing these biomarker improvements.16

The significant change in UACR confirms conventional ARB efficacy. However, concurrent reductions in uNGAL and cystatin C indicate that albuminuria underestimates therapeutic impact. A 2023 trial examining non-albuminuric DN also demonstrated similar biomarker shifts, reinforcing the value of multi-marker monitoring. These findings emphasize more nuanced biopsy-free insight into nephron health.17-20

Repeated measures ANOVA demonstrated a significant time-by-group interaction, indicating persistent divergence between treatment arms over six months. This statistical validation distinguishes true ARB effects from regression to the mean or measurement variability. Methodological rigor, including consistent timing, assay precision, and blinding, lends credibility to results.

Clinically, early ARB initiation grounded in microalbuminuria yet evaluated using tubular and filtration biomarkers may allow preemptive renal protection. This supports emerging practice guidelines advocating biomarker-guided risk modification beyond albuminuria. Such a strategy aligns with the trend toward precision nephrology.

Limitations include relatively short duration, moderate sample size, and absence of hard endpoints such as eGFR decline or onset of macroalbuminuria. The cohort's single-center nature and focus on losartan limit extrapolation. Future larger multicenter trials with longer follow-up and clinical outcome measurements are warranted to validate early biomarker-modulating effects.

Overall, the study supports ARBs' multifaceted renoprotective profile in early DN and suggests incorporation of tubular and filtration biomarkers into early-stage risk assessment. These findings may inform individualized treatment algorithms and stimulate further investigation into biomarker-guided interventions.

Conclusion

Losartan therapy in early-stage diabetic nephropathy favorably reduced key tubular and glomerular injury biomarkers, illustrating renoprotection beyond albuminuria and advocating for early biomarker-informed intervention. Future longitudinal studies should evaluate the prognostic correlation of these biomarker changes with renal outcomes.

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