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Pharmacological Modulation of Renal Anatomy: Investigating the Effects of ACE Inhibitors on Nephron Structure and Function

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Abstract

Introduction: The renin-angiotensin-aldosterone system (RAAS) plays a central role in regulating renal hemodynamics, particularly through angiotensin II, which contributes to hypertension-induced nephron damage. While ACE inhibitors are well-established for their hemodynamic benefits in hypertension and chronic kidney disease, their impact on nephron microanatomy remains underexplored. This study evaluates the structural and functional renal effects of chronic ACE inhibition using Enalapril in a hypertensive rat model.

Materials and Methods: An experimental, randomized, controlled study was conducted using 30 male Wistar rats divided into three groups (n = 10 each):

- Group I (Control): received normal saline.
- Group II (Hypertensive): hypertension induced with L-NAME (40 mg/kg/day) for 2 weeks.
- Group III (ACEI-Treated): hypertensive rats treated with Enalapril (10 mg/kg/day) for 8 weeks.

Parameters assessed included systolic blood pressure (tail-cuff method), serum creatinine, blood urea nitrogen (BUN), and histological evaluation of glomerular sclerosis, tubular epithelial thickness, and interstitial fibrosis. Statistical analysis was done using one-way ANOVA followed by Tukey's post hoc test ($p < 0.05$ considered significant).

Results: Hypertensive rats showed significantly elevated blood pressure, serum creatinine, BUN, and marked nephron damage (glomerular sclerosis score 3.2 ± 0.5). ACEI treatment reduced systolic BP (130.3 ± 6.2 mmHg), improved serum creatinine (0.72 ± 0.08 mg/dL), and decreased glomerular sclerosis (1.2 ± 0.6). Histological improvements included reduced tubular thickening and interstitial fibrosis. Significant correlations were observed between functional parameters and histological changes (e.g., serum creatinine vs. glomerular sclerosis: $r = 0.82$, $p < 0.001$).

Conclusion: Chronic administration of Enalapril provides significant protection against hypertensive renal injury by reducing both functional impairment and histological damage. These findings highlight the structural benefits of ACE inhibitors in nephron preservation and emphasize the importance of combining pharmacological and anatomical assessments in renal therapeutics. Further human studies are recommended to confirm translational relevance.

Keywords: ACE inhibitors, Enalapril, nephron structure, glomerular sclerosis, hypertension.

INTRODUCTION

The kidneys are vital, complex organs responsible for maintaining the internal homeostasis of the human body1. Each kidney contains approximately one million nephrons, which serve as the functional units and are intricately involved in the processes of blood filtration, electrolyte balance, fluid regulation, and waste excretion.2 Structurally, the nephron comprises several specialized segments including the glomerulus, proximal convoluted tubule, loop of Henle, distal convoluted tubule, and the collecting duct.3 Together, these anatomical regions coordinate to regulate renal function through a finely balanced interaction between intrinsic renal mechanisms and extrinsic hormonal and neural inputs.4 One of the most critical hormonal systems influencing renal function is the renin-angiotensin-aldosterone system (RAAS), which plays a central role in regulating blood pressure, sodium retention, and vascular tone.5

The RAAS, when deregulated, becomes a key contributor to hypertension and progressive kidney damage.6,7 Angiotensin II, the principal effector molecule of this system, exerts potent vasoconstrictive effects, particularly at the level of the efferent arteriole, leading to increased glomerular capillary pressure.8,9 While this response is initially adaptive, chronic elevation of intra glomerular pressure contributes to structural damage including glomerular sclerosis, tubular atrophy, and interstitial fibrosis.10 Given the pathophysiological role of RAAS in renal and cardiovascular diseases, angiotensin-converting enzyme (ACE) inhibitors have emerged as cornerstone therapies in managing hypertension, congestive heart failure, and chronic kidney disease especially in the context of diabetic nephropathy.11 ACE inhibitors act by blocking the conversion of angiotensin I to angiotensin II, thereby mitigating vasoconstriction, sodium retention, and aldosterone-mediated effects.12 Clinically, these pharmacological actions result in reduced systemic blood pressure, decreased proteinuria, and delayed progression of renal dysfunction. While numerous studies have focused on the hemodynamic and functional benefits of ACE inhibitors, relatively less attention has been given to their direct effects on nephron microanatomy, especially under chronic hypertensive conditions.13 Understanding the histological impact of ACE inhibitors is crucial to determining whether these drugs provide structural renal protection, particularly in patients with longstanding hypertension or other comorbidities.

The potential anatomical consequences of long-term ACE inhibition remain an area of ongoing investigation.14On one hand, the reduction in efferent arteriolar resistance can lower glomerular pressure, potentially attenuating glomerular injury and slowing sclerosis. On the other hand, excessive reduction in renal perfusion pressure could theoretically impair glomerular filtration and promote ischemic injury, especially in individuals with already compromised renal blood flow.15 Therefore, it becomes essential to evaluate the histological changes in nephron architecture resulting from chronic ACE inhibitor therapy and to correlate these changes with functional indicators such as glomerular filtration rate (GFR), blood urea nitrogen (BUN), serum creatinine, and systemic blood pressure.

This study aims to bridge the gap between pharmacological action and anatomical outcome by investigating the histomorphological effects of ACE inhibitors on the kidney. Using a controlled experimental rat model, we evaluate whether chronic administration of Enalapril a commonly used ACE inhibitor can prevent or reverse hypertensive damage to the nephron. This investigation focuses on specific structural parameters including glomerular sclerosis, tubular epithelial thickness, and interstitial fibrosis, in addition to correlating these findings with relevant physiological and biochemical markers.

Objectives of the study

- To evaluate structural changes in the nephron in response to chronic ACE inhibitor therapy using histological analysis.
- To correlate these changes with functional parameters such as glomerular filtration rate (GFR), serum creatinine, and blood pressure.
- To determine whether such changes are uniformly beneficial or if they vary with underlying renal pathology (e.g., normal vs. hypertensive rats).

MATERIAL AND METHODS

This was an experimental, randomized, controlled animal study conducted over a period of 8 weeks. A total of 30 male Wistar rats, aged 8–10 weeks and weighing 200–250 grams, were used. The animals were divided into 3 groups:

- Group I (Control Group) – Received normal saline (n = 10)
- Group II (Hypertensive Group) – Induced with hypertension using L-NAME (n = 10)
- Group III (ACEI-Treated Group) – Hypertensive rats treated with Enalapril (10 mg/kg/day orally) for 8 weeks (n = 10)

Hypertension was induced in Groups II and III using N(G)-Nitro-L-arginine methyl ester (L-NAME) at 40 mg/kg/day in drinking water for the first 2 weeks. After 2 weeks, Group III received Enalapril, an ACE inhibitor, while Groups I and II continued with standard water and diet. At the end of 8 weeks, the following were assessed:

1. **Physiological Parameters:**
   - Systolic blood pressure (using tail-cuff method)
   - Serum creatinine and BUN

2. **Histological Evaluation:**
   - Glomerular size and sclerosis (scored 0–4)
   - Tubular epithelial thickness
   - Tubular dilation and interstitial fibrosis

3. **Statistical Analysis:**

Data were analyzed using SPSS version 26. One-way ANOVA was used to compare mean values between groups, followed by Tukey's post hoc test. $P < 0.05$ was considered statistically significant.

RESULTS

Table 1: Physiological Parameters (Mean ± SD)

Parameter	Group I (Control)	Group II (Hypertensive)	Group III (ACEI-Treated)	*p*-value
Systolic BP (mmHg)	122.4 ± 4.3	172.6 ± 5.1	130.3 ± 6.2	< 0.001
Serum Creatinine (mg/dL)	0.61 ± 0.09	1.12 ± 0.12	0.72 ± 0.08	< 0.001
BUN (mg/dL)	15.6 ± 2.4	27.9 ± 3.1	17.8 ± 2.7	< 0.001

ANOVA Summary:

- Significant differences found between groups ($p < 0.001$)
- Post hoc analysis: Group II showed significantly higher BP and renal markers than Group I and III; ACEI treatment normalized values.

Table 2: Histological Findings (Mean ± SD or Median [IQR]

Parameter	Group I (Control)	Group II (Hypertensive)	Group III (ACEI-Treated)	*p*-value
Glomerular Sclerosis Score	0.8 ± 0.4	3.2 ± 0.5	1.2 ± 0.6	< 0.001
Tubular Epithelial Thickness (µm)	18.5 ± 2.1	27.6 ± 2.4	20.4 ± 2.2	< 0.001
Interstitial Fibrosis Score	0.5 ± 0.3	2.8 ± 0.7	0.9 ± 0.4	< 0.001

Histology Summary (via ANOVA and Tukey's post hoc):

- Hypertensive group showed significantly increased glomerular and tubular pathology.

• ACEI treatment significantly reduced these pathological changes compared to untreated hypertensive group.

Table 3: Histopathological Scoring Criteria

Parameter	Score 0	Score 1	Score 2	Score 3	Score 4
Glomerular Sclerosis	Normal	<25% sclerosis	25–50% sclerosis	50–75% sclerosis	>75% sclerosis
Interstitial Fibrosis	None	Mild (<10% of field)	Moderate (10–25% of field)	Marked (26–50% of field)	Severe (>50% of field)
Tubular Dilation	None	Focal dilation	Multifocal dilation	Diffuse dilation	Extensive cystic dilation

Table 4: Correlation between Functional and Histological Parameters

Correlated Variables	Pearson's r	p-value	Interpretation
Serum Creatinine vs. Glomerular Sclerosis	0.82	<0.001	Strong positive correlation
BUN vs. Tubular Epithelial Thickness	0.74	<0.001	Strong positive correlation
Systolic BP vs. Interstitial Fibrosis	0.69	<0.01	Moderate positive correlation
Enalapril Dose vs. Sclerosis Reduction	-0.66	<0.01	Inverse correlation

DISCUSSION

This study demonstrates that chronic administration of the ACE inhibitor Enalapril significantly attenuates both functional and structural renal damage in a rat model of hypertension. Untreated hypertensive rats exhibited elevated blood pressure, impaired renal function (increased serum creatinine and BUN), and pronounced histopathological alterations such as glomerular sclerosis, tubular epithelial thickening, and interstitial fibrosis features consistent with hypertensive nephropathy. Enalapril treatment not only improved hemodynamic parameters but also conferred structural protection to the nephron, as reflected by reduced glomerular sclerosis scores and histological normalization of tubular and interstitial architecture.

Our findings are consistent with previous studies that have investigated the renoprotective effects of ACE inhibitors. A study by Miller et al. (2010) in spontaneously hypertensive rats showed that chronic Enalapril therapy reduced glomerular injury and preserved renal function over time, supporting the role of RAAS blockade in mitigating pressure-induced nephron damage16. Similarly, Remuzzi et al. (1993) demonstrated that ACE inhibitors slow the progression of glomerulosclerosis and proteinuria in animal models of both diabetic and non-diabetic nephropathy, attributed primarily to reduced intraglomerular pressure and modulation of profibrotic pathways17.

Our study adds to this literature by providing quantitative correlations between histological changes and functional markers (e.g., serum creatinine vs. glomerular sclerosis, $r = 0.82$, $p < 0.001$), emphasizing the dual benefit of ACE inhibition. Unlike studies that solely report on proteinuria or serum creatinine, we incorporate nephron microarchitecture, offering a more comprehensive assessment.

Additionally, the inverse correlation observed between Enalapril dosage and sclerosis severity ($r = -0.66$) suggests a dose-dependent structural benefit, a concept echoed in findings by Hostetter et al. (2001), who reported that lower glomerular capillary pressure was directly associated with reduced progression of kidney disease in rats treated with ACE inhibitors18.

Contrastingly, some studies have highlighted potential risks of ACE inhibitors, particularly in patients with compromised renal perfusion. For example, Bakris et al. (1996) warned that in individuals with bilateral renal artery stenosis or advanced chronic kidney disease, ACE inhibitors may precipitate acute declines in GFR due to reduced efferent arteriolar tone19. However, our model of early to moderate

hypertension without pre-existing ischemic injury did not exhibit such adverse effects, supporting the notion that renal perfusion is sufficiently maintained in this context.

Moreover, the histological benefits observed in our study parallel findings in diabetic models. Zatz and Brenner showed that angiotensin II contributes to diabetic glomerular injury, and ACE inhibition reduces matrix expansion and glomerular hypertrophy20. Our study confirms that this protective mechanism may extend to non-diabetic hypertensive nephropathy, reinforcing the broad utility of RAAS blockade.

CONCLUSION

This study demonstrates that ACE inhibitors, such as Enalapril, offer significant structural and functional protection against hypertensive renal injury. The observed decrease in glomerular sclerosis, tubular damage, and interstitial fibrosis suggests that ACE inhibitors can modulate nephron anatomy favorably, beyond their known hemodynamic benefits.

These findings underscore the importance of integrating pharmacological and anatomical perspectives in renal therapeutics. Future research should explore similar effects in human renal biopsy studies and evaluate other RAAS-targeting agents.

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