RESEARCH PAPER

A Comparative Study Of Azelnidipine & Telmisartan Vs Amlodipine & Telmisartan For Proteinuria – A Randomized Control Study

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ABSTRACT

Background: Diabetic kidney disease (DKD) is a leading cause of chronic kidney disease in patients with type 2 diabetes mellitus (T2DM) and hypertension. Reduction in urinary albumin–creatinine ratio (UACR) is an established surrogate marker of renal protection.

Aim: To compare the effect of telmisartan–azelnidipine versus telmisartan–amlodipine on proteinuria in patients with T2DM and hypertension (UACR ≥500 mg/g).

Methods: In this prospective, randomised, open-label, parallel-group study, 98 patients were equally allocated to telmisartan–azelnidipine (n = 49) or telmisartan–amlodipine (n = 49). Participants were followed for 90 days with assessments at baseline, 30, 60, and 90 days. The primary outcome was change in UACR; secondary outcomes included changes in systolic (SBP) and diastolic blood pressure (DBP) and safety.

Results: Baseline UACR was comparable (1383.39 ± 779.12 vs 1410.51 ± 1168.69 mg/g; p = 0.558). The telmisartan–azelnidipine group showed a significant reduction in UACR to 439.75 ± 561.27 mg/g at 90 days (mean reduction 943.64 mg/g; p < 0.0001). In contrast, the telmisartan–amlodipine group demonstrated increased UACR to 3524.98 ± 1945.82 mg/g (p < 0.0001). Between-group differences were significant from 30 days onward (p < 0.0001). Both regimens reduced blood pressure; SBP was lower in the intervention group at 30 and 90 days (p = 0.002 and p = 0.006), while DBP differences were not significant. Both treatments were well tolerated.

Conclusion: Telmisartan–azelnidipine showed superior short-term antiproteinuric efficacy compared with telmisartan–amlodipine, despite similar blood pressure control. Larger studies with longer follow-up are needed to confirm long-term renal benefits.

Keywords: Albuminuria; Amlodipine; Calcium Channel Blockers; Diabetic Nephropathy; Hypertension; Telmisartan

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INTRODUCTION

Chronic kidney disease (CKD) represents a major global health burden, particularly among individuals with type 2 diabetes mellitus (T2DM) and systemic hypertension. These conditions frequently coexist and exert synergistic detrimental effects on renal structure and function, accelerating renal injury. This interaction leads to early onset of proteinuria and progressive decline in glomerular filtration rate (GFR).[1]

Proteinuria, defined as increased urinary albumin excretion, is an early marker of diabetic kidney disease (DKD) and an independent predictor of cardiovascular morbidity and mortality.[2] In many patients, albuminuria may precede measurable reductions in GFR. Persistent proteinuria reflects underlying glomerular injury caused by chronic hyperglycemia, oxidative stress, endothelial dysfunction, and increased intraglomerular pressure.[3] Hypertension further exacerbates this process by increasing glomerular capillary pressure, thereby accelerating renal damage.[4]

The progression of DKD is mediated through both hemodynamic and non-hemodynamic mechanisms. Activation of the renin–angiotensin–aldosterone system (RAAS) plays a crucial role by promoting vasoconstriction, aldosterone secretion, and oxidative stress, ultimately worsening renal injury.[5] Therefore, pharmacological strategies targeting blood pressure control and RAAS inhibition are essential to reduce proteinuria and delay renal disease progression.[6]

Telmisartan, an angiotensin receptor blocker (ARB), provides renoprotective effects beyond blood pressure reduction due to its partial peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist activity. This contributes to improved insulin sensitivity, lipid metabolism, and endothelial function, thereby offering both metabolic and renal benefits.[7] Clinical evidence supports its role in reducing urinary albumin excretion and slowing the progression of diabetic nephropathy.[8]

Calcium channel blockers (CCBs) are commonly combined with ARBs to achieve optimal blood pressure control. Amlodipine, a widely used CCB, effectively lowers blood pressure but demonstrates limited antiproteinuric effects compared to agents with additional antioxidant properties.[9] In contrast, azelnidipine, a newer dihydropyridine CCB, exhibits antioxidant and anti-inflammatory actions, reduces heart rate, and improves endothelial function, suggesting enhanced renoprotective potential.[10]

Evidence indicates that azelnidipine, when combined with ARBs, reduces urinary albumin excretion more effectively than conventional regimens, possibly through mechanisms beyond blood pressure

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lowering.[11,12] It is also associated with reduced oxidative stress markers and tubular injury, supporting its role in renal protection.[13,14] Conversely, while the telmisartan–amlodipine combination remains effective and widely used, its antiproteinuric effect appears comparatively modest.[15,16]

Given these differences, identifying the most effective drug combination for reducing proteinuria is essential. This study aims to compare the efficacy of telmisartan–azelnidipine versus telmisartan–amlodipine in reducing proteinuria among patients with T2DM and hypertension, thereby guiding optimal therapeutic strategies in DKD.

MATERIALS AND METHODS

This study was designed as a prospective, randomized, open-label, parallel-group controlled trial conducted at SRM Medical College Hospital & Research Centre. Participants were followed for a period of 3 months (90 days) after initiation of study medication. Written informed consent was obtained from all participants. Confidentiality of patient information was maintained, and participants were free to withdraw at any time without affecting their routine care.

Sample Size calculation

A total of 98 patients were enrolled and randomized in a 1:1 ratio into two groups: intervention group (n = 49) and control group (n = 49). Loss to follow-up occurred during the study period, and the final number of participants analyzed varied at each follow-up visit.

Inclusion & Excluaion Criteria

Patients aged 30–75 years of either sex with diagnosed type 2 diabetes mellitus and systemic hypertension on treatment, and albuminuria ≥500 mg/g assessed by urinary albumin–creatinine ratio (UACR), were included. Patients aged <30 years, pregnant women, those receiving SGLT2 inhibitors (dapagliflozin or canagliflozin), those on antihypertensive agents known to significantly reduce proteinuria, and patients with any condition deemed unsuitable by the investigator were excluded.

Methods

Eligible participants were randomized in a 1:1 ratio into Group A (telmisartan + azelnidipine) and Group B (telmisartan + amlodipine) after eligibility confirmation and informed consent. The study was open-label with no blinding. Group A received telmisartan 40 mg once daily with azelnidipine 8 mg, titrated to 16 mg if target blood pressure (<140/90 mmHg) was not achieved, while Group B received telmisartan 40 mg with amlodipine 5 mg, increased to 10 mg if required. Dose adjustments were permitted to achieve optimal blood pressure control. Other antihypertensive agents known to reduce proteinuria, including ACE inhibitors, additional ARBs, and mineralocorticoid receptor antagonists, were discontinued prior to study initiation. Participants were assessed at baseline, 30, 60, and 90 days with clinical and laboratory evaluations. Loss to follow-up occurred, with 8 participants from each group at 30 days and additional losses in the intervention group at later visits. Data collected included demographic details, medical history, systolic and diastolic blood pressure (SBP, DBP), and urinary albumin–creatinine ratio (UACR). The primary outcome was change in UACR from baseline to 90 days and between-group comparisons at follow-up visits. Secondary outcomes included changes in SBP and DBP, within-group UACR trends, and adverse events. Proteinuria was measured using UACR at all visits, and blood pressure was recorded using standard methods. Participants were monitored for adverse drug reactions, and analysis was performed based on available follow-up data.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies and percentages. The Chi-square test was used for categorical variables. Independent samples t-test was used for between-group comparisons of SBP, DBP, and UACR. Within-group changes in UACR were analysed using repeated measures analysis.

RESULTS

Age and gender distribution were comparable between groups (p = 0.67 and p = 0.152). Most participants were aged 51–60 years (34.7% vs 30.6%) and 61–70 years (26.5% vs 36.7%), with a female predominance (51.0% vs 65.3%) (Table 1).

Table 1: Baseline Characteristics of Study Participants

Variable		Intervention Group (n=49)	Control Group (n=49)	P value
Age Distribution	<40	3 (6.1%)	5 (10.2%)	0.67
	41–50	6 (12.2%)	4 (8.2%)	
	51–60	17 (34.7%)	15 (30.6%)	
	61–70	13 (26.5%)	18 (36.7%)	
	>71	10 (20.4%)	7 (14.3%)	
Gender Distribution	Female	25 (51.0%)	32 (65.3%)	0.152
	Male	24 (49.0%)	17 (34.7%)	

Baseline SBP was higher in the control group (158.73 ± 15.03 vs 151.02 ± 14.18 mmHg; p = 0.01). SBP was significantly lower in the intervention group at Visit 1 (p = 0.002) and Visit 3 (p = 0.006), with a minor reversal at Visit 2 (p = 0.044). DBP decreased in both groups without significant differences (Table 2).

Table 2: Blood Pressure Changes (SBP & DBP) Across Visits

Visit	SBP (Intervention) Mean ± SD	SBP (Control) Mean ± SD	P value	DBP (Intervention) Mean ± SD	DBP (Control) Mean ± SD	P value
Visit 0	151.02 ± 14.18	158.73 ± 15.03	0.01	90.41 ± 12.90	92.65 ± 5.31	0.263
Visit 1	135.85 ± 10.72	144.63 ± 14.16	0.002	88.29 ± 4.42	87.07 ± 6.02	0.299
Visit 2	134.74 ± 5.57	132.44 ± 4.35	0.044	87.89 ± 4.13	89.76 ± 4.74	0.067
Visit 3	140.28 ± 11.83	148.46 ± 12.88	0.006	85.83 ± 7.32	88.97 ± 7.18	0.065

Baseline UACR was similar (p = 0.558). The intervention group showed significantly lower UACR at all follow-ups: Visit 1 (805.59 vs 1975.56), Visit 2 (621.66 vs 2551.12), and Visit 3 (439.75 vs 3524.98 mg/g) (all p < 0.0001) (Table 3).

Table 3: UACR Comparison Between Groups

Visit	UACR (Intervention) Mean ± SD (mg/g)	UACR (Control) Mean ± SD (mg/g)	P value
Visit 0	1383.39 ± 779.12	1410.51 ± 1168.69	0.558
Visit 1	805.59 ± 446.05	1975.56 ± 1498.53	<0.0001
Visit 2	621.66 ± 492.83	2551.12 ± 1647.34	<0.0001
Visit 3	439.75 ± 561.27	3524.98 ± 1945.82	<0.0001

Eight participants from each group were lost at Visit 1; additional losses occurred only in the intervention group at Visit 2 (n = 3) and Visit 3 (n = 2) (Table 4).

Table 4: Loss to Follow-Up Across Visits

Visit	Intervention Group	Control Group
Visit 1	8	8
Visit 2	3	0
Visit 3	2	0

In the intervention group, UACR significantly reduced from baseline to Visit 1 (577.8 mg/g; p = 0.001), Visit 2 (761.73; p < 0.0001), and Visit 3 (943.64; p < 0.0001), with no significant change between Visit 1–2 (p = 0.135). In the control group, significant changes were observed across all intervals (e.g., Visit 0–3: −2114.47; p < 0.0001), indicating poorer UACR control (Table 5).

Table 5: Repeated Measures Analysis of UACR

	Comparison	Mean Difference (mg/g)	P value
Intervention Group	V0–V1	577.8	0.001
	V0–V2	761.73	<0.0001
	V0–V3	943.64	<0.0001
	V1–V2	183.93	0.135
	V1–V3	365.84	<0.0001

	V2–V3	181.91	0.006
Control Group	**Comparison**	**Test Statistic**	**P value**
	V0–V1	-565.05	0.003
	V0–V2	-1140.61	<0.0001
	V0–V3	-2114.47	<0.0001
	V1–V2	-575.56	0.003
	V1–V3	-1549.41	<0.0001
	V2–V3	-973.85	0.003

DISCUSSION

In this randomised controlled study, we compared the effectiveness of telmisartan–azelnidipine versus telmisartan–amlodipine in reducing proteinuria in patients with type 2 diabetes mellitus and hypertension. Baseline characteristics, including age, gender distribution, and UACR, were comparable between groups, although systolic blood pressure (SBP) was slightly higher in the control group, while diastolic blood pressure (DBP) was similar.

The intervention group demonstrated a marked and consistent reduction in UACR, decreasing from 1383.39 mg/g at baseline to 439.75 mg/g at 90 days. In contrast, the control group showed increasing UACR levels during follow-up, from 1410.51 mg/g to 3524.98 mg/g. The between-group difference became significant from Visit 1 onwards ($p < 0.0001$), indicating superior antiproteinuric efficacy of the telmisartan–azelnidipine combination.

Both groups exhibited reductions in blood pressure over time, with no consistent intergroup differences, suggesting comparable antihypertensive efficacy. These findings are supported by previous studies. **Bafna et al.** reported no significant difference in SBP and DBP reduction between azelnidipine and amlodipine ($p > 0.05$).[17] Similarly, **Pal et al.** observed no significant differences in SBP ($p = 0.49$) and DBP ($p = 0.86$), though azelnidipine showed greater heart rate reduction ($p < 0.0001$).[18] **Zhao et al.** also demonstrated effective BP reduction with both drugs, with azelnidipine providing more stable control.[19] These data suggest that the observed renal benefits are not solely attributable to blood pressure reduction.

Repeated measures analysis in the intervention group showed sustained UACR reduction from baseline to Visit 1 (577.80 mg/g; $p = 0.001$), Visit 2 (761.73 mg/g; $p < 0.0001$), and Visit 3 (943.64 mg/g; $p < 0.0001$), with a non-significant change between Visit 1 and Visit 2 ($p = 0.135$). In contrast, the control group demonstrated significant variations with an overall increasing trend in UACR, indicating poorer proteinuria control.

The increase in UACR in the control group despite BP reduction suggests that blood pressure control alone may not sufficiently influence short-term renal outcomes. This emphasises the importance of drug selection in patients with diabetic kidney disease. The superior effect of azelnidipine may be related to additional mechanisms such as antioxidant, anti-inflammatory, and endothelial protective actions.

These findings are consistent with previous evidence. **Tewari et al.** reported significant UACR reduction with azelnidipine ($p = 0.003$) along with heart rate reduction.[14] **Takenaka et al.** observed greater proteinuria reduction with azelnidipine compared to amlodipine (–38% vs –29%; $p < 0.01$).[20] Similarly, **Nakamura et al.** demonstrated significant improvement in urinary protein excretion with azelnidipine but not with amlodipine.[21] These studies support the enhanced renoprotective profile of azelnidipine.

Amlodipine, however, remains an effective antihypertensive agent with proven safety. Studies by **Quan et al.** and **Fogari et al.** have shown that telmisartan–amlodipine combinations can reduce albuminuria.[9,15] Although the magnitude of reduction appears less pronounced. Amlodipine is also associated with dose-dependent adverse effects such as peripheral oedema, which may affect adherence.[22,23]

The combination of telmisartan and azelnidipine offers complementary effects. Telmisartan provides RAAS blockade and metabolic benefits, while azelnidipine contributes antioxidant and vascular protective effects, along with stable blood pressure control and reduced sympathetic activation.[24] These combined effects may explain the superior reduction in UACR observed in this study.

Despite comparable blood pressure control, the greater reduction in proteinuria with the telmisartan–azelnidipine combination suggests additional renoprotective mechanisms beyond hemodynamic effects. These may include reduced oxidative stress and improved endothelial function, although these were not directly assessed.

Limitations

The relatively short duration of follow-up (3 months) limits assessment of long-term renal outcomes such as changes in glomerular filtration rate (GFR). The sample size was modest, which may affect the generalizability of findings. The open-label design may introduce potential bias. Variability in UACR measurements and loss to follow-up could have influenced the results. Further large-scale studies with longer follow-up are required to validate these findings.

CONCLUSION

The telmisartan–azelnidipine combination resulted in a significant and sustained reduction in UACR over the study period, whereas the telmisartan–amlodipine group showed comparatively higher UACR levels during follow-up. Both regimens effectively reduced blood pressure. The reduction in UACR was significantly greater in the azelnidipine group, indicating superior short-term antiproteinuric efficacy in patients with T2DM and hypertension. However, longer follow-up is required to evaluate long-term renal outcomes before definitive clinical recommendations can be made.

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