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Research Article

Retrospective Study to Assess the Effect of Telmisartan on Urine Albumin-To-Creatinine Ratio (UACR) in Indian Hypertensive Patients with Diabetes

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Abstract

Introduction: Hypertension (HTN) is one of the major causes of Chronic Kidney Disease (CKD). Impaired kidney function and kidney damage can be detected by albuminuria. This study was aimed at assessing the effect of Telmisartan monotherapy on urine albumin-to-creatinine ratio (UACR) among Indian hypertensive patients.

Materials and Methods: This was a retrospective cohort study. Data was collected retrospectively from 161 centres across India between Feb 2015 to Feb 2021. Hypertensive patients on Telmisartan monotherapy with UACR records available of at least two analyzable visits were enrolled. Demographic, clinical, treatment and outcome data of hypertensive patients meeting the inclusion criteria were captured. Mean changes in UACR and blood pressure (BP) from visit 1 to visit 2 were assessed.

Results: Data of 1095 patients was available for analysis. The mean age was 54.0±11.7 years with 615 males and 480 females. The mean interval between Visit 1 and 2 was 278.06 days with a mean UACR 113.58 mg/g at Visit 1 and 77.29 mg/g at Visit 2 (mean difference of -36.29 mg/g, p=0.0012). The mean UACR in diabetic patients (n=945) was 83.3±312.4 mg/g at visit 1 and 58.27±231.47 mg/g at visit 2 (difference -25.02 mg/g, p=0.0055, mean duration 292.06 days). The mean systolic BP at visit 1 and visit 2 was 142.23 and 133.71 mm/Hg (mean change -8.5 mm/Hg, p<0.001) and the mean diastolic BP at visit 1 and visit 2 was 83.77 and 80.04 mm/Hg (mean change -3.8 mm/Hg, p<0.001) respectively.

Conclusion: Telmisartan can effectively reduce UACR and BP in Indian patients. It can be a promising treatment option to delay the progression of proteinuria in hypertensive patients.

Keywords: Albuminuria; HTN; Telmisartan; UACR

Introduction

Systemic arterial hypertension (HTN) is a global health problem and is also one of the most important modifiable risk factors for all-cause morbidity and mortality worldwide. It is associated with increased cardiovascular and renal morbidity [1] and also represents the leading risk factor for death in the world. It is attributed to cause an estimated 7.5 million deaths a year (13% of all deaths) [2]. According to estimates, 31.1 percent of adults (1.39 billion) in the world had HTN in 2010. Adult HTN was more common in low- and middle-income nations (31.5 percent, or 1.04 billion persons) as compared to high-income nations (28.5 %, 349 million people). [3]

HTN is one of the major causes responsible for chronic kidney disease (CKD). It has been noted that long-term uncontrolled HTN leads to increased intraglomerular pressure and causes damage to glomerulus as well as glomerular filtration. This results in abnormally increased amounts of protein in the urine termed as proteinuria. [4] Adequate control of arterial blood pressure plays a crucial role in slowing down the progression of CKD. The kidney damage of a CKD patient can be detected with the help of albuminuria and kidney function according to the glomerular filtration rate (GFR). The levels of albuminuria can be stated as Normal: <30 mg/d, Microalbuminuria: 30-300 mg/d and Macroalbuminuria: >300 mg/d [5]. The severity of albuminuria correlates with blood pressure (BP) levels and responds to the lowering of BP. Microalbuminuria refers to slight increase in urine albumin excretion and is linked to the consequences of long-term primary HTN. It is usually associated with signs of cardiovascular damage including left ventricular hypertrophy and carotid plaques or thickening [6]. Thus, microalbuminuria has a powerful predictive value for cardiovascular and renal events. Evaluating patients for an increase in urine albumin excretion has become a useful way to evaluate overall cardiovascular risk in routine clinical practice, especially in patients with HTN and diabetes [7].

The activation of renin-angiotensin-aldosterone system (RAAS), especially angiotensin-2 is involved in CKD pathogenesis and its cardiovascular complications. The drugs interfering with the renin-angiotensin system, such as angiotensin II receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEIs) are of choice in patients with HTN and CKD. ACEIs/ARBs have a blood pressure-independent anti-proteinuric effect. With ACE inhibitors, the complete RAAS inhibition is prevented due to the formation of angiotensin II using non-ACE pathways. However, ARBs overcome this limitation by selective blockade of the angiotensin 1 (AT1) receptor and therefore angiotensin II escape observed with an ACEI does not occur with an ARB. [8,9] A prospective cohort study indicated that in patients with advanced CKD and stable HTN, antihypertensive treatment with ACEIs or ARBs reduces the likelihood of long-term dialysis and lowers the mortality risk as well. [10,11] ARBs reduce protein excretion by approximately 35% to 40%, which is greater than other antihypertensive agents. [12] Reduction in proteinuria correlates with slowing the progression of kidney disease.

Telmisartan is an ARB which is increasingly prescribed due to its good tolerability, cardio metabolic benefits, longer half-life of 24 hours and once daily dosing. [13] Telmisartan has been examined for its effects on decreasing BP and urine albumin-to-creatinine ratio (UACR) with promising findings. This study was conducted to assess the effect of Telmisartan on UACR and BP among Indian hypertensive patients on Telmisartan monotherapy.

Materials and methods

Study Design: This was a retrospective cohort study, in which the data was collected from 16 Feb 2015 to 02 Feb 2021 from 20 states that included 64 cities, and informed consent was not required. Data from all eligible hypertensive patients who were prescribed with Telmisartan (20mg, 40mg, or 80mg orally once daily) monotherapy was collected after obtaining approval from the ethics committee (Suraksha Ethics committee. Reg No: ECR/644/Inst/MH/2014/RR-17). Data collection and analysis were performed from an Indian electronic software owned and administered by HealthPlix Technologies PRV. Longitudinal information including demographics, diagnosis, medications, cardiac risk factors, tests conducted, and other data elements obtained from the software were used to conduct the analysis. The study confirms the applicable national regulatory laws and guidelines. Patient confidentiality was always maintained, and the study was performed using anonymized information only. The Electronic Medical Records were reviewed for the patients fulfilling all the inclusion criteria for eligibility.

Study Population: Inclusion and Exclusion Criteria - The hypertensive patients of age at least 18 years at the time of baseline assessment and who have been prescribed Telmisartan as monotherapy without modification of treatment, having two distinct UACR values on two visits were included in the study. The patients who stopped Telmisartan prematurely (non-compliance) without medical advice or patients on combination therapy for the treatment of HTN were excluded from the study.

Assessment criteria: The following parameters were assessed during the study and thus were the basic criteria for the final assessment:

- Changes in UACR between two analyzable visits.
- Change in systolic and diastolic blood pressure between two analyzable visits.

- Changes in UACR in diabetic hypertensive patients between two analyzable visits.

Sample Size Calculation: Makino H et al [14], in their study on telmisartan observed that UACR changed from 172±47.5 mg/g to 136±124 mg/g at end of the study. Assuming that similar changes in UACR will be observed in Indian patients, α of 0.05, power of 95% (β = 0.05) we got a sample size of 616 patients**.** If about 40% of the data might not fulfill the criteria of the study, data of additional 246 patients (40% of 616) would be screened. Thus, final sample size was 862 patients. However, considering the retrospective nature of the study we aimed to collect data of maximum possible patients.

Statistical Analysis: The mean change in UACR and the mean change in BP (systolic and diastolic) from visit 1 to visit 2 were compared using paired t-test.

Results

The study enrolled a total of 1095 patients, 945 of whom were diagnosed with Diabetes Mellitus (DM). The average age was 54.0 ± 11.7 years with 615 males and 480 females. 173 had an ideal BMI, 262 were over-weight and 182 were obese. The demographic characteristics of the patients are presented in Table 1.

Parameter	Category	Patient count (n)
Patient Distribution	Patients enrolled	1095
	Patients with DM	945
Age (Years)	18-39 years	123
	40-64 years	768
	≥65 years	204
Gender	Male	615
	Female	480
Geographic Distribution	Class 1 (> 1 lakh)	281
	Class 2-4 (> 10,000- 1 lakh)	4
	Metro (>10 lakh)	810
	Rural (<10,000)	0
BMI (Kg/m^2)	BMI <25	173
	BMI 25-29.9	262
	BMI ≥30	182

Table 1: Baseline demographic characteristics of the patients.

A total of 983 patients were available for BP analysis, with 260 receiving 20 mg, 682 receiving 40 mg, and 41 receiving 80 mg of Telmisartan. The details of all the patients who were reviewed in this study are provided in table 2.

Description of patient population	Patient count (n)
Total Patients (≥18 years old) in EMR on Telmisartan at visit 1 with two analyzable visits having UACR values	1095
Total Patients (≥18 years old) on Telmisartan at visit 1 with two analyzable visits having UACR values and co-diagnosed with DM	945
Total patients considered for UACR assessment	1095
Total patients considered for BP assessment (BP readings available at baseline and follow-up visit)	983
Total Patients with HTN considered for BP assessment (BP readings available at baseline and follow-up visit) and co-diagnosed with Diabetes Mellitus	843

Table 2: Details of the count of the patients whose electronic medical records (EMR) were reviewed in the study.

Effect of Telmisartan on UACR in the overall population (1095 patients)

The mean interval between Visit 1 and Visit 2 was 278.06 days. The mean UACR was 113.58 mg/g at Visit 1 and 77.29 mg/g at Visit 2, with a mean difference of -36.29 mg/g (p=0.0012) between the two visits, as shown in Table 3, Figure 1. These results clearly show that monotherapy with Telmisartan is linked with a considerable decrease in UACR from visit 1 to visit 2.

	Interval between Visit 1 and Visit 2 (days)	Mean UACR (mg/g)		The difference in values between 2 visits
		Visit-1	Visit-2	
Mean	278.06	113.58	77.29	-36.29
Standard Deviation (SD)	187.38	443.74	326.76	
Number of patients (n)	1095.00	1095	1095	
P-Value			0.0012	

Table 3: The mean UACR values (mg/g) at visit 1 and visit 2 for all 1095 patients.

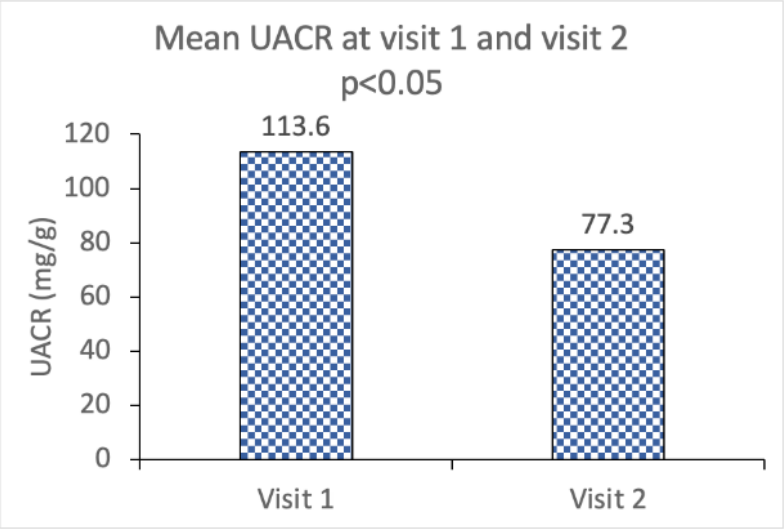

Figure 1: The change in mean UACR (mg/g) from visit 1 to visit 2 in overall population.

Effect of Telmisartan on UACR in patients with DM and HTN (945 patients)

The mean interval between Visit 1 and Visit 2 was 292.06 days. The mean UACR was 83.3 mg/g at Visit 1 and 58.27 mg/g at Visit 2, with a mean difference of -25.02 mg/g (p=0.0055) between the two visits, as shown in **Table 4**. These results clearly show that monotherapy with Telmisartan is associated with a significant decrease in UACR in patients with DM and HTN from visit 1 to visit 2. In addition, a significant decrease in HbA1c (p=0.0019) was also observed between visit 1 and visit 2 (**Figure 2**).

	Interval between Visit 1 and Visit 2 (days)	Mean UACR (mg/g)		The difference in values between 2 visits
		Visit-1	Visit-2	
Mean	292.06	83.3	58.27	-25.02
SD	185.70	312.4	231.47	
P-Value			0.0055	

Table 4: The mean UACR values (mg/g) at visit 1 and visit 2 in patients with DM and HTN.

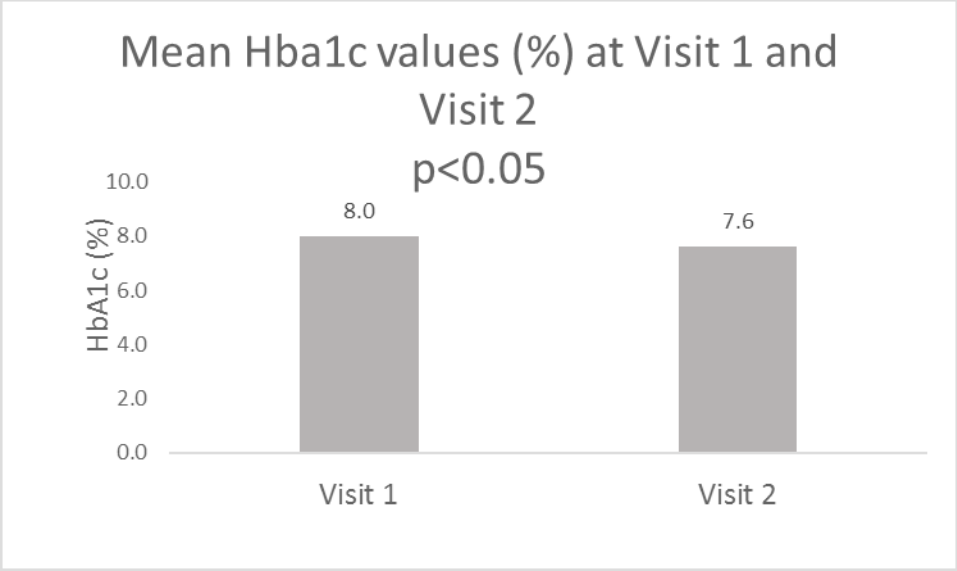

Figure 2: The change in mean HbA1c (%) from visit 1 to visit 2 in patients with DM and HTN.

Table 5 shows the percentage of patients in whom the UACR was reduced to <30mg/g at visit 2. 34.15% patients achieved UACR <30 mg/g in Visit 2.

UACR Range (mg/g)	Total patients in range	Patients achieving the UACR <30mg/g in Visit 2, n(%)
30-300	256	107 (41.8%)
>300	72	5 (6.94%)
Total	328	112 (34.15%)

Table 5: Percentage of patients achieving UACR <30mg/g at Visit 2.

Effect of Telmisartan on BP (overall population, n=983)

The mean duration of the interval between Visit 1 and Visit 2 was 99.6 days. The Mean Systolic BP (SBP) at visit 1 and visit 2 was 142.23 and 133.71 mmHg (mean change -8.5, p<0.001) and the mean diastolic BP (DBP) at visit 1 and visit 2 was 83.77 and 80.04 mmHg (mean change -3.8, p<0.001) respectively as shown in **Table 6**. There was a statistically significant reduction in SBP and DBP from visit 1 to visit 2.

	Interval between Visit 1 and Visit 2	Mean SBP at Visit 1 (mmHg)	Mean SBP at Visit 2 (mmHg)	Difference of mean SBP between 2 Visits	Mean DBP at Visit 1 (mmHg)	Mean DBP at Visit 2 (mmHg)	Difference of mean DBP between 2 Visits
Mean	99.61	142.23	133.71	-8.5	83.77	80.04	-3.8
SD	92.26	14.01	15.76		9.65	8.78	
Count	983	983	983		983	983	
P-Value				<0.001			<0.001

Table 6: The mean BP values (Systolic and Diastolic) (mmHg) at visit 1 and visit 2.

Effect of Telmisartan on BP in patients with DM and HTN (843 patients)

The mean duration of the interval between Visit 1 and Visit 2 was 101.5 days. The Mean SBP at visit 1 and visit 2 was 142.40 and 133.71 mmHg (mean change -8.7, p<0.001) and the mean DBP at visit 1 and visit 2 was 83.60 and 79.80 mmHg (mean change -3.8, p<0.001) respectively as shown in **Table 7.** There was a statistically significant reduction in SBP and DBP from visit 1 to visit 2.

	Interval between Visit 1 and Visit 2	Mean SBP at Visit 1 (mmHg)	Mean SBP at Visit 2 (mmHg)	Difference of mean SBP between 2 Visits	Mean DBP at Visit 1 (mmHg)	Mean DBP at Visit 2 (mmHg)	Difference of mean DBP between 2 Visits
Mean	101.50	142.40	133.7	-8.7	83.6	79.8	-3.8
SD	92.39	14.10	16		9.7	8.7	
Count	843	843	843		843	843	
P-Value				<0.001			<0.001

Table 7: The mean BP values (Systolic and Diastolic) (mmHg) at visit 1 and visit 2 in patients with DM and HTN.

Discussion

This retrospective cohort study aimed to analyse the effect of Telmisartan on UACR and BP among Indian hypertensive patients through electronic medical records. The results showed a significant reduction in UACR and BP in overall population as well as in patients with DM and HTN.

Ogawa H et al, in a multicentre, open-label, randomized study, compared the effects of Telmisartan with those of non-ARB standard therapy on UACR changes for three years from the start of antihypertensive treatment (ATTEMPT-CVD study). By 36 months it was found that, despite similar BP control in both arms, UACR had decreased by 12.2 mg/gCr in the Telmisartan group compared to a decrease of 4.1 mg/gCr in the non-ARB group (P<0.001). [15]

Agrawal A et al conducted a prospective observational study which evaluated effects of Telmisartan on kidney function in patients with chronic kidney disease (n=55, 96.36% hypertensive; 63.61% diabetic). After three months of treatment with Telmisartan, 24-h urinary protein, spot urine protein-to-creatinine, serum creatinine and BP significantly reduced (p<.05) by 806.78 mg, 0.95, 0.44 mg/dl and 8.9/4.7mmHg in the overall population. [16]

A meta-analysis done in Japan reviewed data from 20 controlled prospective trials and concluded that Telmisartan is likely beneficial in improving proteinuria/albuminuria. This meta-analysis pooled data from more than 25000 patients. A significant percent reduction was observed in urinary protein excretion / urinary albumin excretion / urinary protein to creatinine ratio / urinary albumin to creatinine ratio in the 7 ARB-control [mean difference (MD), − 19.99%; 95% CI, − 28.68% to − 11.30%; p < 0.00001], 7 ACEI-control (MD, − 14.08%; 95% CI, − 25.36% to − 2.80%; p = 0.01), 6 non-ARB/ACEI-control (MD, − 39.82%; 95%

CI, − 55.96% to − 23.69%; $p < 0.00001$), and all the 20 trials (MD, − 24.36%; 95% CI, − 32.85% to − 15.87%; $p < 0.00001$). [17]

In a prospective study, Fujino N. et al. investigated whether Telmisartan reduces the UACR in hypertensive patients. From baseline to 6 months, there were significant reductions in UACR 26.6 ± 26.9 vs. 14.3 ± 16.5 mg/g, SBP 146.8 ± 8.5 vs. 131.2 ± 12.8 mmHg and DBP 85.8 ± 10.4 vs. 77.1 ± 7.2 mmHg with treatment of Telmisartan. [18]

Makino H et al studied prevention of transition from incipient to overt nephropathy with Telmisartan in patients with Type 2 Diabetes in a randomized, multicenteric, double-blind, placebo controlled trial with mean duration of 1.3±0.5 years (n=527, 163 normotensive). It was found that with treatment of Telmisartan 80 mg and 40 mg, mean UACR decreased by 58.8 mg/g and 37.9 mg/g respectively. Placebo increased UACR by 40.9 mg/g (both telmisartan doses vs. placebo, $P < 0.0001$). SBP/DBP decreased from 138/78 mmHg to 128/72 mmHg with 80 mg telmisartan and from 137/78 mmHg to 128/72 mmHg with 40 mg telmisartan (each BP change at 1 year from baseline $P < 0.01$). [19]

UACR is one of the key markers for CKD. Albuminuria changes could indicate how well patients are responding to treatment and how likely they are to progress. A greater UACR at the time of diagnosis was linked to an increased risk of renal events, such as loss of half of eGFR, dialysis, or mortality, in the CRIC (The Cohort Study of Chronic Renal Insufficiency) study. [20] RAAS system plays a key role in the pathophysiology of progressive kidney disease. It is known that ARBs are used to delay the onset and curtail the duration of nephropathy. AMADEO study has proven the efficacy of Telmisartan in reducing proteinuria in hypertensive patients with diabetic nephropathy as a part of the programme of research to show Telmisartan's End-organ protection (PROTECTION). [21]

In the current study, Telmisartan provided significant reductions in UACR in addition to BP reductions in hypertensive patients including those having diabetes. There were also 34.15% patients having UACR reduced to <30 mg/g with Telmisartan treatment. This evidence provides notion about the anti-proteinuric effect of Telmisartan in Indian hypertensive and diabetic patients which needs to be further confirmed in randomized clinical trials.

Retrospective design is one of the limitations of this study which may have led to selection bias due to unknown confounding factors. The methods used for UACR assessment were not available and they may be different from different labs. There were wide variations in data leading to larger standard deviations (particularly duration between 1st and 2nd UACR and BP records) and BP records were not available for all patients at baseline and subsequent visit.

Conclusion

Telmisartan can effectively reduce UACR as well as systolic and diastolic BP in Indian patients with HTN including those with diabetes. It can be a promising treatment option to delay the progression of proteinuria in the Indian population with HTN.

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Conflicts of Interest: Dr Hanmant Barkate, Dr Sachin Suryawanshi, Dr Mayur Jadhav and Dr Prashant Mishra are employees of Glenmark Pharmaceuticals Limited. Dr Balram Sharma, Dr Mohan Magdum, Dr Ashok Jhingan and Dr Jay Shah do not have any conflicts of interest.

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