International Journal of Advances in Medicine
Giri R et al. Int J Adv Med. 2019 Feb;6(1):140-145
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20190120

Original Research Article

Anti-albuminuric effects of spironolactone and its effect along with ramipril in type-2 diabetic nephropathy

Richa Giri, Ashish Naresh*, J. S. Kushwaha, Brijesh Kumar, R. K. Verma, Mohd. Imran Khan

Department of Medicine, GSVM Medical College, Kanpur, Uttar Pradesh, India

Received: 07 December 2018
Accepted: 02 January 2019

***Correspondence:**
Dr. Ashish Naresh,
E-mail: ashishnaresh6@gmail.com

ABSTRACT

Background: The study was conducted to evaluate and compare the protective effects of spironolactone (alone) and its effects along with ACE inhibitor (ramipril) on diabetics (30-70year) in relation to proteinuria and state of diabetic nephropathy.
Methods: A comparative, prospective, non-randomized, non-blinded experimental study was conducted on 56 patients (30-70year) of diagnosed type 2 diabetes mellitus showing proteinuria. Total duration of study was about one year from October 2017 to October 2018. Patients were divided in two groups, group A (n=28, spironolactone 25mg and ramipril 5mg) and group B (n=27, spironolactone 25mg). Subjects were followed over 12weeks and baseline and 12-week urine ACR being compared.
Results: Both the group after receiving respective drug were followed for 3month duration and response were assessed by measuring urine ACR value at end of 3months. Mean values of baseline and follow up urine ACR for group A and group B were 471.5±465.62, 244.66±237.54 and 474.88±438.94, 268.42±268.16 respectively, P value found to be >0.05 at 95%C.I. It was observed that percentage reduction of urine ACR were 48% and 43.47% in group A and group B respectively.
Conclusions: In the study, it was concluded that spironolactone had significant effect over proteinuria reduction over follow up period in patient with diabetic nephropathy though there was no additional statistically significant advantage of addition of spironolactone and ACE inhibitor over proteinuria reduction. Significant reduction of proteinuria occurred in both group A and group B over 12weeks follow up period, 48 % reduction in group A and 43.47% in group B. This difference proved statistically not significant after applying independent t-test.

Keywords: ACE-Angiotensin converting enzyme, ACR-Albumin creatinine ratio

INTRODUCTION

Diabetic nephropathy (DN) is a progressive kidney disease caused by damage to the capillaries in the kidney's glomeruli. It is due to longstanding diabetes mellitus and is a prime reason for dialysis in many developed countries. It is classified as a small blood vessel complication of diabetes. Nephropathy is diagnosed by the persistent presence of elevated urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR) or other manifestations of kidney damage. DKD (Diabetic Kidney disease) or CKD attributed to diabetes occurs in 20-40% of patients with diabetes. DKD typically develops after diabetes duration of 10years in type 1 diabetes but may be present at diagnosis of type 2 diabetes. DKD can progress to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation and is the leading cause of ESRD. In addition, among people with type 1 or type 2 diabetes, the presence of CKD markedly increases cardiovascular risk.

Screening for diabetic nephropathy must be initiated at the time of diagnosis in patients with type 2 diabetes, since ~7% of them already have microalbuminuria at that time, if microalbuminuria is absent, the screening must be repeated annually for both type 1 and 2 diabetic patients.[1]

Early detection and treatment of diabetic nephropathy will reduce the progression to end stage renal disease (ESRD). Intensive glucose and blood pressure control reduces proteinuria, slows renal dysfunction and protects against microvascular complications. IRMA-2 (Irbesartan in Micro-albuminuria, type-2 diabetic nephropathy trial) provided evidence that Angiotensin Receptor Blockers (ARBs) prevent the progression of microalbuminuria to macroalbuminuria in diabetic nephropathy.

Urinary albumin excretion (albuminuria) is one of the important risk factors for the progression of renal disease to ESRD. Therefore, control of microalbuminuria can slow down the progression of nephropathy.[2]

Interruption of renin-angiotensin-aldosterone system by angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) and renin inhibitors can be extremely helpful for decelerating the progression of renal disease but after a while, the aldosterone level (the last product of the renin-angiotensin-aldosterone system) increases to its original level due to the aldosterone escape phenomenon. This phenomenon that occurs in about 40% of patients with diabetic nephropathy, usually happens in long-term ACEIs and ARBs consumers.[3,4]

Aldosterone acts as a renal injury mediator through inflammation induction, fibrosis and necrosis in the kidney tissue. It is assumed that aldosterone reduces the BNP7 expression, and down-regulation of BMP7 expression is one of the early events in diabetic nephropathy. Therefore, it is proposed that usage of ACEIs and ARBs alone cannot prevent the aldosterone effects.[5] Adjuvant therapy with aldosterone receptor blockers such as spironolactone can be effective for the albuminuria improvement.[6-9]

The objectives were to evaluate and compare the protective effect of spironolactone (alone) and its effect along with ACE inhibitor (ramipril 5mg) on diabetics (30-70yr) in relation to proteinuria and state of diabetic nephropathy.

METHODS

Study was conducted on 64 patients (30-70yr) of diagnosed type 2 diabetes mellitus showing proteinuria (according to ADA). Patients after screening were selected for study and 32 patients were given spironolactone (25mg OD) along with ramipril 5mg and 32 patients were given spironolactone (25mg OD) alone and were followed up at 6weeks to measure the safety of drugs administered and finally followed up at 12weeks to record the final follow up urine ACR values and serum potassium level. Study subjects were taken from IPD and OPD of KPS Institute of Medicine, LLR hospital, GSVM medical college Kanpur and prior consent was obtained before the start of study. Initially there were total 64 patients out of which 9 patients did not came for follow up, hence total 55 patients were included in the study.

It is a hospital based experimental study conducted over patients of diagnosed type 2 diabetes mellitus with proteinuria. Detailed history was taken by direct interview, clinical examination was performed, relevant laboratory investigation was done and data was recorded on the case sheet.

Inclusion criteria followed in study were age 30-70years, diagnosed type 2diabetes mellitus, serum potassium level <5meq/l, estimated GFR >30ml/min/1.73m^2 and HbA1c <10%. Exclusion criteria were type 1 diabetes mellitus, impaired glucose tolerance secondary to endocrine disease, exocrine pancreatic disease, SBP >180mmHg DBP >110mmhg, UTI, haematuria, acute febrile illness, vigorous exercise, short-term pronounced hyperglycemia, obstructive uropathy, confirmed or suspected renal artery disease by USG doppler study, serum potassium level >5.5meq/l, congestive heart failure, prior myocardial infarction or stroke during preceding six month and female patient-who are pregnant, breast feeding, planning for pregnancy.

Follow-up visits were conducted every consecutive 6weeks for any adverse drug effects. Final follow up values were recorded at 12weeks from the starting point of study. Physical examination, blood pressure and serum creatinine and potassium levels will be obtained at 6week and 12weeks to check the safety of drugs given. As a rule, for safety, a decision was made to discontinue the study for any patient whose serum potassium level will be >5.5mEq/L and eGFR calculated by serum creatinine (by Cockcroft gault formula) decreased >30% from the starting level.

Patients after screening were selected for study and the first 32 patients chronologically were given spironolactone (25mg OD) along with ramipril 5mg and subsequent 32 patients were given spironolactone (25mg OD) and were followed up at 6weeks to measure the safety of drugs administered and finally followed up at 12weeks to record the final follow up urine ACR values and serum potassium level.

Base line urine ACR values for both the groups were compared at follow up urine ACR values at 12weeks. Other base line laboratory investigation such as serum lipid profile, HbA1c, eGFR, fundus examination, ultrasonography (KUB), serum urea, serum creatinine, haemoglobin, were taken at the starting point.

Data obtained from the two study groups were compiled and tabulated and continuous variables are expressed as

mean±SD. To evaluate baseline characteristics, comparisons of each continuous parameters between group A and group B were performed with the independent t-test and P value being calculated at C.I 95%.

RESULTS

In this study, total 64 patients with type 2 diabetes mellitus suffering from diabetic nephropathy were enrolled in the study. During the screening phase, patients were selected according to the inclusion criteria and exclusion criteria (discussed in material and method) then eligible patients were entered into the treatment phase. Among these 64 patients, 55 patients were included in the study and total 9 patients excluded because of poor compliance and follow up. The mean age of patients who took part in study was 53.87±9.51years. Among 64 patients, 37 (57%) were male and 27 (43%) were females.

Study subjects were then subdivided in to two study group i.e. group A and group B as per enrolment in study, first 30 patients were allotted group and subsequently enrolled 34 patients were allotted group B. The mean age of patient in group A was 55.37±8.96 compared to the mean age of patient in group B were 52.46±10.24 (Table 1 shows baseline characteristics of two groups).

Table 1: Baseline characteristics of two groups.

Variables	Group A (mean±SD)	Group B (mean±SD)	P value
Age (years)	55.37±8.96	52.46±10.24	0.25
HbA1c (%)	7.91±1.34	8.31±1.42	0.28
S. urea (mg/dl)	55.70±25.98	78.78±40.80	0.01
S. creatinine (mg/dl)	1.50±0.67	2.02±1.07	0.03
S. Tgl (mg/dl)	163.33±59.22	172±75.54	0.63
S. LDL (mg/dl)	108.81±85.01	92.35±40.37	0.36
S. HDL (mg/dl)	49.42±11.96	51.47±18.19	0.62
Blood sugar (mg)	185.77±58.11	184.35±55.10	0.92
eGFR (ml/min/1.73m^2)	111.8±22.5	110.5±23.6	0.64
Urine ACR	471.5±465.62	474.88±438.9	0.97
S. potassium	4.24±0.59	4.07±0.61	0.29

Of total 64 patient, 28 (44%) were in microalbuminuria (urine ACR 30-300) and 36 (56%) were in overt proteinuria (>300) range. In group A, 16 (59%) were in microalbuminuria and 11 (41%) were showing overt proteinuria. In group B, total 13 (46%) patient had microalbuminuria and 15 (54%) had overt proteinuria.

After evaluating base line characteristics follow-up visits were conducted every consecutive 6weeks for any adverse drug effects. Final follow up values were recorded at 12weeks from the starting point of study. Physical examination, blood pressure and serum creatinine and potassium levels will be obtained at 6week and 12weeks to check the safety of drugs given. As a rule, for safety, a decision was made to discontinue the study for any patient whose serum potassium level will be >5.5mEq/L and eGFR calculated by serum creatinine decreased >30% from the starting level. Both the group after receiving respective drug were followed for 3month duration and response were assessed by measuring urine ACR value at end of 3months.

Mean value of urine ACR at start of study for group A 471.5±465.62 as compared to mean value of group B were 474.88±438.94. P value found to be >0.05 at 95%CI, which denotes that there was no significant difference between value of base line urine ACR of both groups (Table 2).

Table 2: Base line and 12week urine ACR mean value with SD in group A and group B.

	Group A	Group B	P value
Base line U. ACR	471.5±465.62	474.88±438.94	0.97
Follow-up U. ACR	244.66±237.54	268.42±268.16	0.72

For base line U. ACR t cal=0.028, C.I 95%, p value >0.05.
For follow up U. ACR t cal = 0.347, C.I 95%, p value >0.05.

After follow-up period urine ACR, mean value at 12week for group A 244.66±237.54 as compared to group B 268.42±268.16. P value found to be >0.05 at 95%CI, which denotes that there was no significant difference between value of follow up Urine ACR of both groups (Table 2).

After applying independent t test for mean value of base line and follow up urine ACR value between both group P value found to be >0.05at 95%CI, which denotes that there was no significant difference between value of base line and follow up urine ACR of both groups (Figure 1).

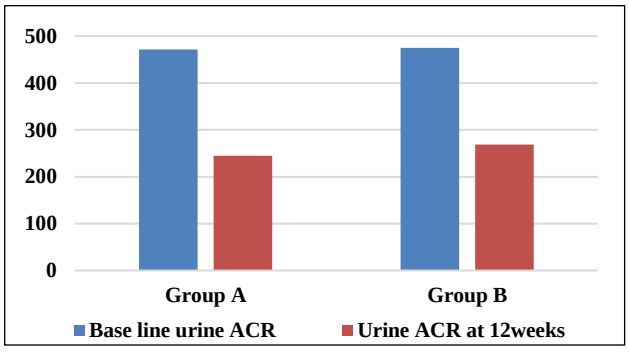

Figure 1: Correlation between baseline and follow-up U. ACR in both groups.

For comparing effects with in a group paired t-test was applied separately in each group, t calculated was found more that value of t observed with p value <0.05 which

proved statistically significant and denotes that there was significant reduction of proteinuria over 12weeks follow up period in both the group (Figure 2).

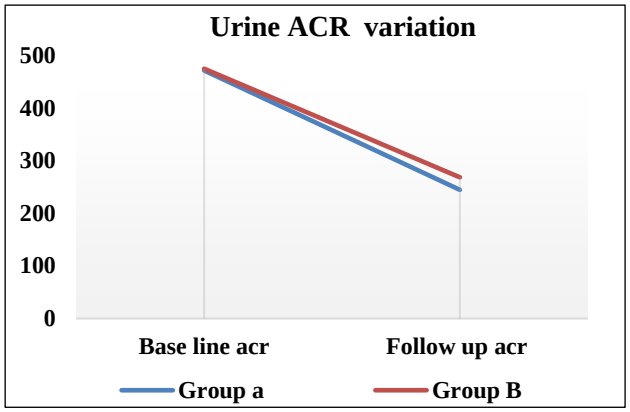

Figure 2: The linear reduction in the mean urine ACR values in subjects of group A and group B after 12weeks follow-up.

There were total 27 patients in group A who were on tab spironolactone (25mg) OD along with tab ramipril (5mg) od where the percentage reduction in the urine ACR values after 12weeks follow-up was found to be 48% from the base line values whereas there were total 28 patients in group B who were given tab spironolactone (25mg) where the percentage reduction was found to be 43.47% (Figure 3).

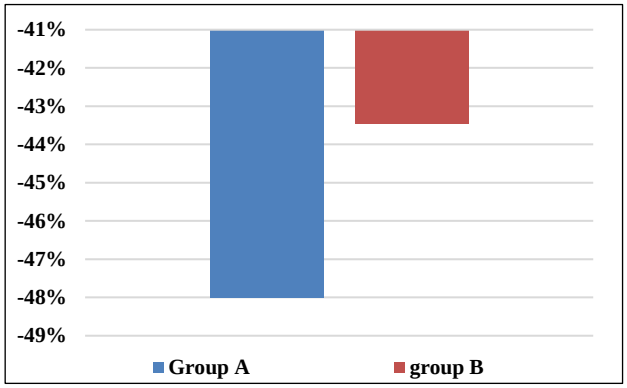

Figure 3: Percentage reduction in urine ACR in group A and group B.

DISCUSSION

It was observed that, both study groups were similar in all baseline characteristics except for values of serum urea and serum creatinine which were significantly differ in both group (p value<0.05 at CI 95%), higher in group B patients. Both groups were then followed for next 12weeks and serial changes in values of urine ACR and serum potassium were assessed.

Mean value of urine ACR at start of study for group A 471.5±465.62 as compared to mean value of group B were 474.88±438.94. P value found to be >0.05 at 95%C. I, which denotes that there was no significant difference between value of base line urine ACR of both groups.

After follow-up period urine ACR mean value at 12week for group A 244.66±237.54 as compared to group B 268.42±268.16. P value found to be >0.05 at 95%CI, which denotes that there was no significant difference between value of follow up urine ACR of both groups. Though percentage decline in urine ACR were more in group A (48%) as compared to percentage decline in group B which was 43.47% but this difference proved statistically not significant after applying independent t-test at CI of 95%.

For comparing effects with in a group paired t-test was applied separately in each group, t calculated was found more that value of t observed with p value <0.05 which proved statistically significant and denotes that there was significant reduction of proteinuria over 12weeks follow up period in both the group. In this study, author found that in diabetic patients, treatment with spironolactone alone has the same effect as combination therapy with spironolactone and Ramipril on urine ACR reduction.

Similar percentage reduction in urine ACR were found in study be Kato S et al, who followed fifty-two Japanese patients with diabetic nephropathy and albuminuria (100 mg/gCr-2000mg/gCr) treated with renin–angiotensin system (RAS) blockade were enrolled in a prospective, randomized, open-label study. The patients were subjected to add-on treatment with spironolactone 25mg once daily and compared with matched controls for 8weeks. At end, they observed that albuminuria was reduced by 33% (9% confidence interval: 22-54; P=0.0002) at 8weeks with spironolactone. This percentage reduction was comparable to this study in which 43.47% reduction in urine ACR were found at end of 12weeks in subject receiving spironolactone.[10]

Almost similar results were also reported by Davidson M et al, studied effect of spironolactone therapy on albuminuria in patients with type 2 diabetes treated with angiotensin-converting enzyme inhibitors. Twenty-four patients with type-2 DM and albuminuria completed the study. Eleven patients had microalbuminuria and 13 had macroalbuminuria. Following treatment with spironolactone, urinary albumin excretion dropped from a mean+/-SD of 404.6+/-60.9mg/d to 302.7+/-52.7mg/d (25.7% decrease, P<.001). In the microalbuminuria and macroalbuminuria groups, the urinary albumin excretion dropped 27.2% (P=0.05) and 24.3% (P=0.02), respectively. Final conclusion of study was stated that spironolactone was effective in further decreasing albuminuria in patients with type 2 DM who are already treated with ACE inhibitors.[11]

Mavrakanas TA et al, in systemic review study observe that Mineralocorticoid receptor blockade in addition to angiotensin converting enzyme inhibitor or angiotensin II receptor blocker treatment further reduced albuminuria

by 23 to 61% compared with standard treatment.[12] In study by Bianchi S et al, evaluate the short-term (8weeks) effects of spironolactone on proteinuria in 42 patients with chronic kidney disease (CKD) already treated with ACE inhibitors and/or ARBs. Spironolactone (25mg/d for 8weeks) decreased proteinuria from protein of 2.09+/0.16 to 1.32+/-0.08g/24 h after 2weeks and 1.05+/-0.08 g/24h after 8weeks. Four weeks after discontinuation of spironolactone therapy, proteinuria returned to close to baseline values. Baseline proteinuria correlated significantly with plasma aldosterone level (r=0.81; P <0.0001). This study shows that spironolactone may effectively reduce proteinuria in patients with CKD.[13]

Study performed by Chrysostomou A et al, also supported this study, it was observed that on addition of spironolactone to ACE inhibitor in patient with CRF, there was a 54 percent reduction in protein excretion (mean±SD value before spironolactone treatment, 3.81±2.50g per day, mean value after treatment, 1.75±1.02g per day), which were comparable to this study.[14]

CONCLUSION

In the study, it was concluded that spironolactone had significant effect over proteinuria reduction over follow up period in patient with diabetic nephropathy though there was no additional statistically significant advantage of addition of spironolactone and ACE inhibitor over proteinuria reduction. Significant reduction of proteinuria was occurred in both group A and group B over 12weeks follow up period, 48% reduction in group A and 43.47% in group B. This difference proved statistically not significant after applying independent t test. This study had some limitations, population was small and the level of microalbuminuria was different between the two groups before the intervention but it was not statistically significant. Follow-up period of study should be long enough to comment on safety profile of combining spironolactone and ACE inhibitors in diabetic nephropathy patients. Microalbuminuria is itself a risk factor for cardio vascular event, which could not be assessed during short period of study, so to comment on cardiovascular mortality and morbidity further longer duration of follow up needed.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR, et al. Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Inter. 2003;63(1):225-32.
2. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405-12.
3. Schjoedt KJ, Andersen S, Rossing P, Tarnow L, Parving HH. Aldosterone escape during blockade of the renin-angiotensin-aldosterone system in diabetic nephropathy is associated with enhanced decline in glomerular filtration rate. Diabetol. 2004;47(11):1936-9.
4. Sato A, Hayashi K, Naruse M, Saruta T. Effectiveness of aldosterone blockade in patients with diabetic nephropathy. Hypertension. 2003;41(1):64-8.
5. Greene EL, Kren S, Hostetter TH. Role of aldosterone in the remnant kidney model in the rat. J Clin Investigation. 1996;98(4):1063-8.
6. Chrysostomou A, Becker G. Spironolactone in addition to ACE inhibition to reduce proteinuria in patients with chronic renal disease. New Eng J Med. 2001;345(12):925-6.
7. Rachmani R, Slavachevsky I, Amit M, Levi Z, Kedar Y, Berla M, et al. The effect of spironolactone, cilazapril and their combination on albuminuria in patients with hypertension and diabetic nephropathy is independent of blood pressure reduction: a randomized controlled study. Diab Med. 2004;21(5):471-5.
8. Rossing K, Schjoedt KJ, Smidt UM, Boomsma F, Parving HH. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: a randomized, double-masked, cross-over study. Diab Care. 2005;28(9):2106-12.
9. Bianchi S, Bigazzi R, Campese VM. Antagonists of aldosterone and proteinuria in patients with CKD: an uncontrolled pilot study. Am J Kidney Dis. 2005;46(1):45-51.
10. Kato S, Maruyama S, Makino H, Wada J, Ogawa D, Uzu T, et al. Anti-albuminuric effects of spironolactone in patients with type 2 diabetic nephropathy: a multicenter, randomized clinical trial. Clin Exp Nephrol. 2015;19(6):1098-106.
11. Davidson M, Wong A, Hamrahian A, Stevens M, Siraj E. Effect of spironolactone therapy on albuminuria in patients with type 2 diabetes treated with angiotensin-converting enzyme inhibitors. Endocrine Prac. 2008;14(8):985-92.
12. Mavrakanas TA, Gariani K, Martin PY. Mineralocorticoid receptor blockade in addition to angiotensin converting enzyme inhibitor or angiotensin II receptor blocker treatment: an emerging paradigm in diabetic nephropathy: a systematic review. Euro J Inter Med. 2014;25(2):173-6.
13. Bianchi S, Bigazzi R, Campese VM. Antagonists of aldosterone and proteinuria in patients with CKD:

an uncontrolled pilot study. Am J Kidney Dis. 2005;46(1):45-51.
14. Chrysostomou A, Becker G. Spironolactone in addition to ACE inhibition to reduce proteinuria in patients with chronic renal disease. New Eng J Med. 2001;345(12):925-6.

Cite this article as: Giri R, Naresh A, Kushwaha JS, Kumar B, Verma RK, Khan MI. Anti-albuminuric effects of spironolactone and its effect along with ramipril in type-2 diabetic nephropathy. Int J Adv Med 2019;6:140-5.