Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com/journal/sjams/home

OPEN ACCESS

Medicine

Anti-Albuminuric Effects of Spironolactone In Type -2 Diabetic Nephropathy

Dr. Richa Giri[1], Dr. Ashish Naresh[2*], Dr. J.S.Kushwaha[3], Dr. Brijesh Kumar[4], Dr.R.K.Verma[5], Dr. Mohommed Imran Khan[6]

[1]M.D. (Medicine), Professor and Head, Department of Medicine, GSVM Medical College, Kanpur, Uttar Pradesh, India
[2]Junior Resident, Department of Medicine, GSVM Medical College, Kanpur, Uttar Pradesh India
[3]M.D. (Medicine), Professor, Department of Medicine, GSVM Medical college, Kanpur, Uttar Pradesh, India
[4]M.D. (Medicine), Associate Professor, Department of Medicine, GSVM Medical College, Kanpur, Uttar Pradesh, India
[5]Senior resident, Department of Medicine, GSVM Medical College, Kanpur, Uttar Pradesh, India

***Corresponding author:** Dr. Ashish Naresh
| **Received:** 06.01.2019 | **Accepted:** 17.01.2019 | **Published:** 30.01.2019
DOI: 10.36347/sjams.2019.v07i01.047

Abstract | **Original Research Article**

Background: The study was conducted to evaluate the protective effects of Spironolactone on diabetics (30-70yr) in relation to proteinuria and state of Diabetic Nephropathy. ***Material methods:*** A comparative, prospective, non-randomized, non-blinded experimental study was conducted on 32 patients (30-70yr) of diagnosed Type 2 Diabetes Mellitus showing proteinuria. Total duration of study was about one year from October 2017 to October 2018. Subjects were followed over 12 weeks and baseline and 12-week Urine ACR being compared. Initially there were total 32 patients out of which 4 patients did not came for follow up, hence total 28 patients were included in the study. Base line Urine ACR values were compared with follow up Urine ACR values at 12 weeks. 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. ***Observations:*** Patients after receiving drug (spironolactone 25mg) were followed for 3-month duration and response were assessed by measuring urine ACR value at end of 3 months. Mean values of baseline and follow up Urine ACR for Group was 474.88±438.94, 268.42±268.16 respectively For comparing effects ,paired t test was applied , t calculated was found more that value of t observed with p value <0.05 which proved statistically significant and denotes that there were significant reduction of proteinuria over 12 week follow up period in. It was observed that percentage reduction of Urine ACR was 43.47%. ***Conclusions:*** In the study it was concluded that spironolactone had significant effect over proteinuria reduction over follow up period in patient with diabetic nephropathy. Significant reduction of proteinuria(43.47%) occurred over 12 weeks follow-up period.

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

INTRODUCTION

Diabetic nephropathy (DN) is a progressive kidney disease caused by damage to the capillaries in the kidneys' 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 10 years 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].

Objectives

To evaluate and compare the protective effect of Spironolactone on diabetics (30-70yr) in relation to proteinuria and state of Diabetic Nephropathy

MATERIALS AND METHODS

Study was conducted on 32 patients (30-70yr) of diagnosed Type 2 Diabetes Mellitus showing proteinuria (according to ADA). Patients after screening were selected for study and given Spironolactone (25mg OD) and were followed up at 6 weeks to measure the safety of drugs administered and finally followed up at 12 weeks 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 32 patients out of which 4 patients did not came for follow up, hence total 28patients 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 < 5 meq/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 hyperglycaemia, 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 6 weeks for any adverse drug effects. Final follow up values were recorded at 12 weeks from the starting point of study. Physical examination, blood pressure and serum creatinine and potassium levels will be obtained at 6 week and 12 weeks 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 given Spironolactone (25mg OD) and were followed up at 6 weeks to measure the safety of drugs administered and finally followed up at 12 weeks to record the final follow up Urine ACR values and serum potassium level.

Base line Urine ACR values were compared with follow up Urine ACR values at 12 weeks. 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.

Statistical analysis

Data obtained from the study groups were compiled and tabulated and Continuous variables are expressed as mean ± SD. For comparing effects, paired t test was applied and t calculated was compared with t observed.

OBSERVATIONS

In our study total 32 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 32 patients, 28 patients

were included in the study and total 4 patients excluded because of poor compliance and follow up. The mean age of patients who took part in study was 52.5±10.2years. Among 28 patients, 16 (57.1%) were males and 12(42.9%) were females. Of total 28 patient, 15 (54%) were in microalbuminuria (Urine ACR 30-300) and 13 (46%) were in overt proteinuria (>300). (Table 1 shows baseline characteristics of study group.)

After evaluating base line characteristics Follow-up visits were conducted every consecutive 6 weeks for any adverse drug effects. Final follow up values were recorded at 12 weeks from the starting point of study. Physical examination, blood pressure and serum creatinine and potassium levels will be obtained at 6 week and 12 weeks 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 3-month duration and response were assessed by measuring urine ACR value at end of 3 months.

Mean value of urine ACR at start of study were 474.88±438.94. After follow-up period urine ACR mean value at 12week were268.42±268. 16 (table 2). For comparing effects with in a group paired t test is applied ,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 12 weeks follow up period in the group (figure 1).

There were total 28 patients in group who were on tab Spironolactone (25mg) where the percentage reduction in the Urine ACR values after 12 weeks follow up was found to be 43.47% from the base line values (figure 2).

Table-1: Shows baseline characteristics of study group.

Variables	(mean±**SD)**
Age (years)	52.46±10.24.
HbA1c(%)	8.31±1.42
S.urea(mg/dl)	78.78±40.80
S.creatinine(mg/dl)	2.02±1.07
S.Tgl(mg/dl)	172±75.54
S.LDL(mg/dl)	92.35±40.37
S.HDL(mg/dl)	51.47±18.19
Blood sugar (mg)	184.35±55.10
eGFR(ml/min/1.73m$^{2)}$	110.5±23.6
Urine ACR	474.88±438.94
s. potassium	4.07±0.61

Table-2: Base line and 12-week urine ACR mean value with SD

	Base line U.ACR	Follow up ACR	Paired t test
Spironolactone group	474.88±438.94	268.42±268.16	P<0.05

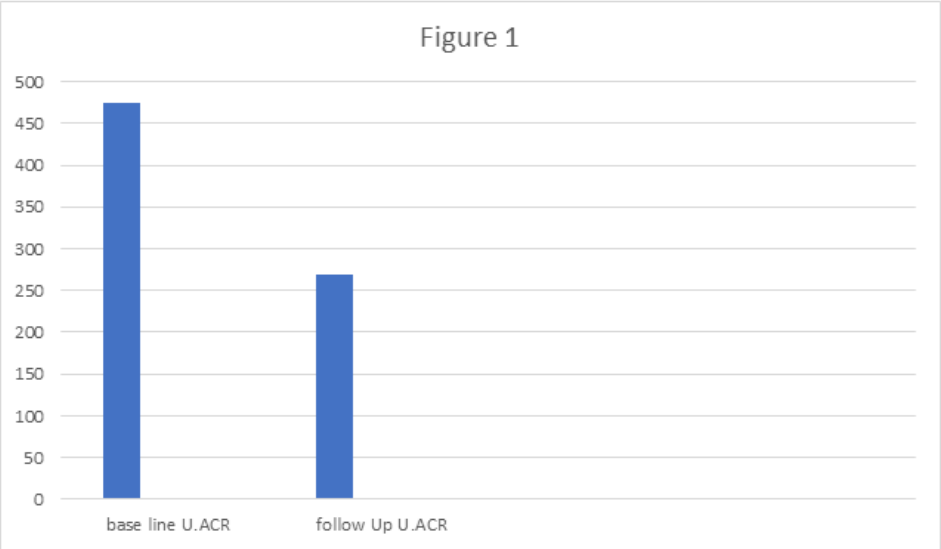

Fig-1: Showing correlation between baseline and follow up U.ACR

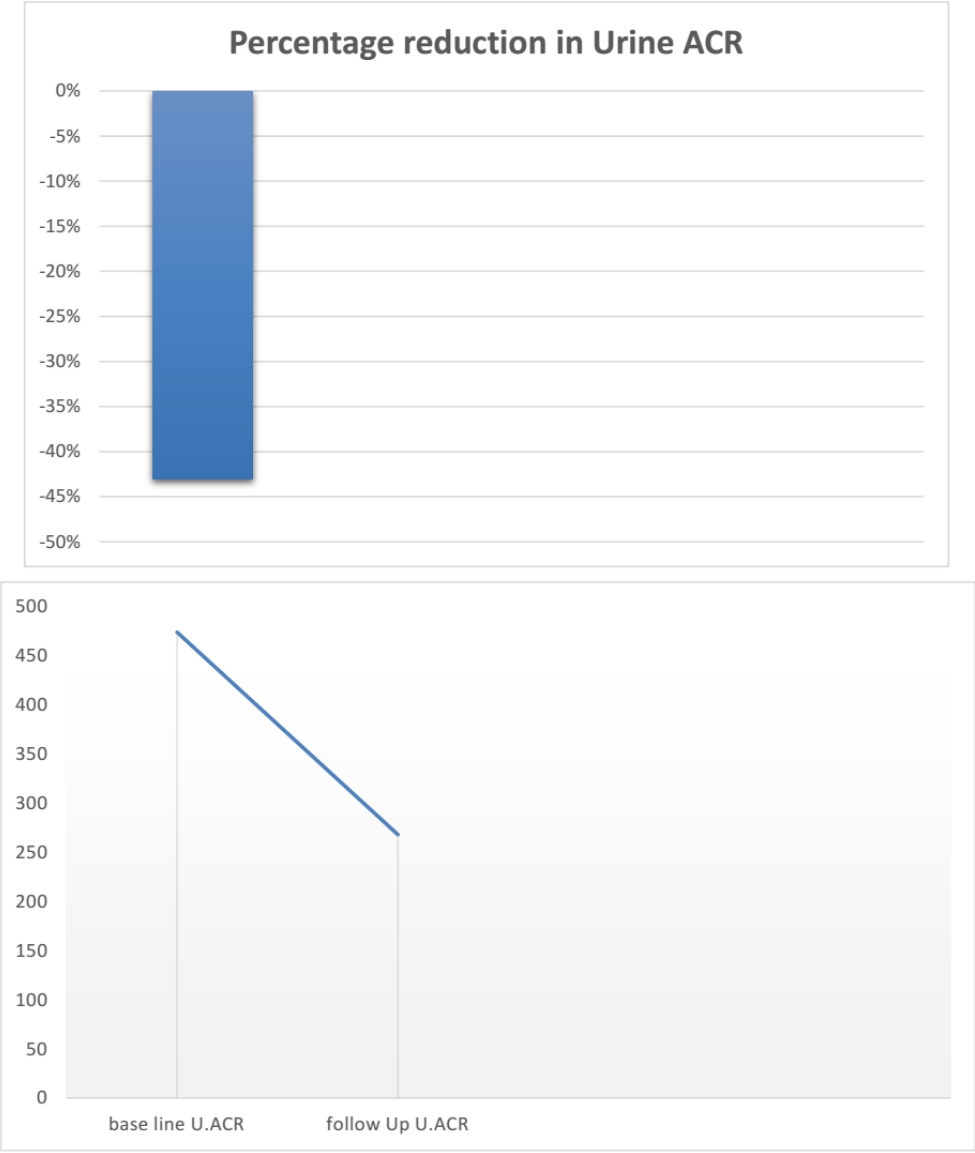

Fig-2: Showing the linear reduction in the mean urine ACR values in subjects after 12 weeks follow-up

DISCUSSION

After follow-up period urine ACR mean value at 12week was 268.42±268. 16. P value found to be <0.05 at 95%C. I, which denotes that there was significant difference between values of follow up Urine ACR.

For observing effects with in a group paired t test is applied, 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 12 weeks follow up period in study population. In this study, we found that in diabetic patients, treatment with spironolactone alone has significant effect over proteinuria reduction. Though safety profile need to be assessed over longer follow up period.

Similar percentage reduction in urine ACR were found in study be Sawako Kato, Shoichi Maruyama, Hirofumi Makino, *et al*. in 2015 who followed Fifty-two Japanese patients with diabetic nephropathy and albuminuria (100 mg/gCr–2000 mg/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 25 mg once daily and compared with matched controls for 8 weeks. At end they observed that Albuminuria was reduced by 33% (9 % confidence interval: 22–54; P = 0.0002) at 8 weeks with spironolactone. This percentage reduction was comparable to our 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 MB, Wong A, Hamrahian AH *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 +/- 60.9 mg/d to 302.7 +/- 52.7 mg/d (25.7% decrease, P<.001). In the microalbuminuria and macroalbuminuria groups, the urinary albumin excretion dropped 27.2% (P = .05) and 24.3% (P = .02), respectively. Final conclusion of study was stated that Spironolactone is effective in further decreasing albuminuria in patients with type 2 DM who are already treated with ACE inhibitors [11].

Mavrakanas TA, Gariani K *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, Bigazzi R *et al*. evaluate the short-term (8 weeks) effects of spironolactone on proteinuria in 42 patients with chronic kidney disease (CKD) already treated with ACE inhibitors and/or ARBs. Spironolactone (25 mg/d for 8 weeks) decreased proteinuria from protein of 2.09 +/- 0.16 to 1.32 +/- 0.08 g/24 h after 2 weeks and 1.05 +/- 0.08 g/24 h after 8 weeks. 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*. studied also support our study in 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±2.50 g per day; mean value after treatment, 1.75±1.02 g per day), which were comparable to our study [14].

CONCLUSIONS

In the study it was concluded that spironolactone had significant effect over proteinuria reduction over follow up period in patient with diabetic nephropathy. Significant reduction of proteinuria was occurred over 12 weeks follow up period, 43.47% in study group. This study had some limitations, population was small and Follow up period of study should be long enough to comment on safety profile of spironolactone in diabetic nephropathy patients. The antialbuminuric effect of spironolactone should be compared with conventional ACEi/ARBs theraoy. 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.

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