



ISSN: 0975-833X

Available online at <http://www.journalcra.com>

INTERNATIONAL JOURNAL
OF CURRENT RESEARCH

International Journal of Current Research
Vol. 11, Issue, 02, pp.1348-1351, February, 2019

DOI: <https://doi.org/10.24941/ijcr.34256.02.2019>

RESEARCH ARTICLE

ANTI-ALBUMINURIC EFFECTS OF SPIRONOLACTONE ALONG WITH RAMIPRIL IN TYPE-2 DIABETIC NEPHROPATHY

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ARTICLE INFO

Article History:

Received 14th November, 2018
Received in revised form
30th December, 2018
Accepted 09th January, 2019
Published online 28th February, 2019

Key Words:

ACR - Albumin creatinine ratio
ACE - Angiotensin converting enzyme
HbA1c- Glycosylated haemoglobin
eGFR- estimated glomerular filtration rate.

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Citation: Dr. Richa Giri, Dr. Ashish Naresh, Dr. Kushwaha, J.S., Dr. Saurabh Agrawal, Dr. Brijesh Kumar and Dr. Verma, R.K. 2019. "Anti-albuminuric effects of spironolactone along with ramipril in type-2 diabetic nephropathy", *International Journal of Current Research*, 11, (02), 1348-1351.

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 (Adler *et al.*, 2003). 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 (Stratton *et al.*, 2000). 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 (Schjoedt *et al.*, 2004; Sato *et al.*, 2003). 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 (Greene, 1996). Adjuvant therapy with aldosterone receptor blockers such as spironolactone can be effective for the albuminuria improvement (Chrysostomou, 2001; Rachmani *et al.*, 2004; Rossing *et al.*, 2005; Bianchi, 2005).

Objectives: To evaluate the protective effect of Spironolactone along with Ramipril 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) along with Ramipril 5mg 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 5 patients did not come for follow up, hence total 27 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 2 Diabetes Mellitus, Serum potassium level < 5 meq/l, Estimated GFR > 30 ml/min/1.73m² and HbA1c $< 10\%$. Exclusion criteria were Type 1 Diabetes Mellitus, Impaired glucose tolerance secondary to endocrine disease, exocrine pancreatic disease, SBP > 180 mmhg, DBP > 110 mmhg, 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 > 5.5 meq/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 > 5.5 meq/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) along with Ramipril 5mg 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 \pm 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, 27 patients were included in the study and total 5 patients excluded because of poor compliance and follow up. The mean age of patients who took part in study was 55.37 ± 8.96 years. Among 27 patients, 16 (59.2%) were males and 11 (40.8%) were females. Of total 27 patients, 16 (59%) were in microalbuminuria (Urine ACR 30-300) and 11 (41%) were in overt proteinuria (> 300). (Table 1 shows baseline characteristics of two groups.) 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 > 5.5 meq/L and eGFR calculated by serum creatinine decreased $> 30\%$ from the starting level. Study subjects after receiving respective drug were followed for 3-month duration and response were assessed by measuring urine ACR value at end of 3 months.

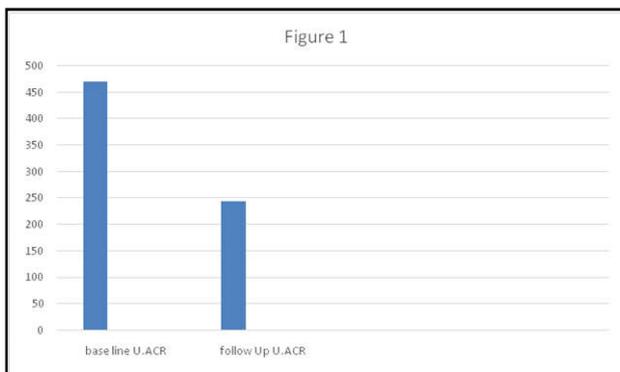
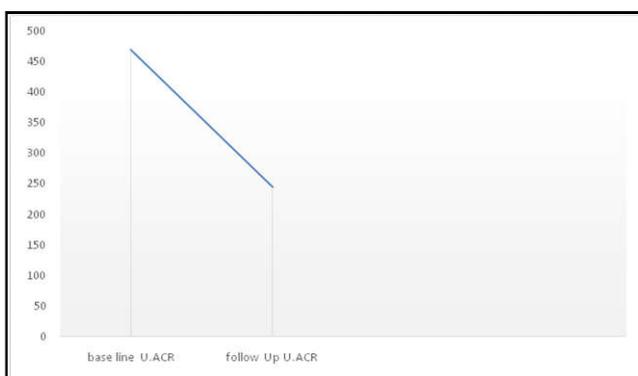
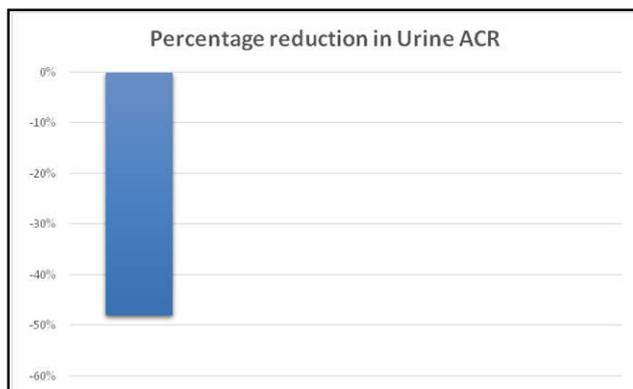
Mean value of urine ACR at start of study were 471.5 ± 465.62 . After follow-up period urine ACR mean value at 12 week were 244.66 ± 237.54 (Table 2) For comparing effects with in a group paired t test is applied, t calculated was found more than value of t observed with p value < 0.05 which proved statistically significant and denotes that there was significant reduction of proteinuria over 12 weeks follow up period in the group (Figure 1). There were total 27 patients in group who were on tab Spironolactone (25mg) along with Ramipril 5mg where the percentage reduction in the Urine ACR values after 12 weeks follow up was found to be 48% from the base line values (Figure 2)

RESULTS AND DISCUSSION

After follow-up period urine ACR mean value at 12 week was 244.66 ± 237.54 P value found to be < 0.05 at 95% C. I, which denotes that there was significant difference between value of

Table 1. Shows baseline characteristics of two groups

Variables	(mean±SD)
Age (years)	55.37±8.96
HbA1c(%)	7.91±1.34
S.urea(mg/dl)	55.70±25.98
S.creatinine(mg/dl)	1.50±0.67
S.Tgl(mg/dl)	163.33±59.22
S.LDL(mg/dl)	108.81±85.01
S.HDL(mg/dl)	49.42±11.96
Blood sugar (mg)	185.77±58.11
eGFR(ml/min/1.73m ²)	115.6±23.5
Urine ACR	471.5±465.62
s. potassium	4.24±0.59

**Figure 1. Showing correlation between baseline and follow up U.ACR****Figure 2. Showing the linear reduction in the mean urine ACR values in subjects after 12 weeks follow-up**

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 needs to be assessed over longer follow up period. Similar percentage reduction in urine ACR were found in study by 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 (Sawako Kato *et al.*, 2015). Almost similar results were also reported by Davidson (2008) 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 (Davidson *et al.*, 2008).

Mavrakanas *et al.* (2014) 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 (Mavrakanas *et al.*, 2014). In study by Bianchi *et al.* (2005) 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 (Bianchi *et al.*, 2005). Study performed by Chrysostomou *et al.* (2001) 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 (Chrysostomou, 2001).

Conclusions

In the study it was concluded that combining spironolactone with Ramipril 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, 48% 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 adding spironolactone with Ramipril in diabetic nephropathy patients. The antialbuminuric effect of spironolactone along with Ramipril should be compared with conventional ACEi/ARBs therapy. 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.

REFERENCES

- Adler AI., Stevens RJ., Manley SE., Bilous RW., Cull CA., Holman RR. 2003. Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int* 63:225–232.
- Bianchi S., Bigazzi R., Campese VM. 2005. Antagonists of aldosterone and proteinuria in patients with CKD: an uncontrolled pilot study. *Am J Kidney Dis.*,
- Bianchi S., Bigazzi R., Campese VM. 2005. Antagonists of aldosterone and proteinuria in patients with CKD: an uncontrolled pilot study. *Am J Kidney Dis.*, 46(1):45–51.
- Chrysostomou A., Becker G. 2001. Spironolactone in addition to ACE inhibition to reduce proteinuria in patients with chronic renal disease. *N Engl J Med.*, 345(12):925–6. doi: 10.1056/nejm200109203451215.
- Chrysostomou A., Becker G. 2001. Spironolactone in addition to ACE inhibition to reduce proteinuria in patients with chronic renal disease. *N Engl J Med.*, 345(12):925–6. doi: 10.1056/nejm200109203451215.
- Davidson MB., Wong A., Hamrahian AH., Stevens M., Siraj ES. 2008. Effect of spironolactone therapy on albuminuria in patients with type 2 diabetes treated with angiotensin-converting enzyme inhibitors. *Endocr Pract.*, 14(8):985–92.
- Greene EL., Kren S., Hostetter TH. 1996. Role of aldosterone in the remnant kidney model in the rat. *J Clin Invest.* 98(4):1063–8. doi: 10.1172/jci118867.
- Mavrakanas TA., Gariani K., Martin PY. 2014. 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. *Eur J Intern Med.*, 25: 173–176.
- Rachmani R., Slavachevsky I., Amit M., Levi Z., Kedar Y., Berla M. *et al.*, 2004. 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. *Diabet Med.*, 21(5):471–5. doi: 10.1111/j.1464-5491.2004.01194
- Rossing K., Schjoedt KJ., Smidt UM., Boomsma F., Parving HH. 2005. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: a randomized, double-masked, cross-over study. *Diabetes Care.*, 28(9):2106–12
- Sato A., Hayashi K., Naruse M., Saruta T. 2003. Effectiveness of aldosterone blockade in patients with diabetic nephropathy. *Hypertension.* 41
- Sawako Kato, Shoichi Maruyama, Hirofumi Makino, Jun Wada, Daisuke Ogawa, Takashi Uzu, Hisazumi Araki, Daisuke Koya, Keizo Kanasaki, Yutaka Oiso, Motomitsu Goto, Akira Nishiyama, Hiroyuki Kobori, Enyu Imai, Masahiko Ando, Seiichi Matsuo. 2015. Anti-albuminuric effects of spironolactone in patients with type 2 diabetic nephropathy: a multicenter, randomized clinical trial. *Clinical and Experimental Nephrology* 19, 1098-1106.
- Schjoedt KJ., Andersen S., Rossing P., Tarnow L., Parving HH. 2004. Aldosterone escape during blockade of the renin-angiotensin-aldosterone system in diabetic nephropathy is associated with enhanced decline in glomerular filtration rate. *Diabetologia.*, 47(11):1936–9. doi: 10.1007/s00125-004-1542-0.
- Stratton IM., Adler AI., Neil HA., Matthews DR., Manley SE., Cull CA., Hadden D., Turner RC., Holman RR. 2000. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412.
