

## Original Research Article

# Effect on serum potassium level in patients of diabetic nephropathy on spironolactone and ramipril over follow up period

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### ABSTRACT

**Background:** The study was conducted to evaluate the change in serum potassium level over follow up period in patients of diabetic nephropathy on spironolactone (25 mg) and ramipril (5 mg) and compare the results with diabetic nephropathy patients on Spironolactone (25 mg) alone.

**Methods:** A comparative, prospective, non-randomized, non-blinded experimental study was conducted on 56 patients (30-70 yr.) of diagnosed type 2 diabetes mellitus showing proteinuria. Total duration of study was about one year from October 2017 to October 2018. Inclusion criteria followed in study were Age 30-70 years, diagnosed type 2 diabetes mellitus, serum potassium level <5 meq/l, estimated GFR >30 ml/min/1.73m<sup>2</sup> 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, hematuria, acute febrile illness, vigorous exercise, short-term pronounced hyperglycemia, obstructive uropathy, confirmed or suspected renal artery disease by USG doppler study, Serum potassium level >5.5 meq/l. Patients were divided in two groups, group A (n= 28, spironolactone 25 mg and ramipril 5 mg) and group B (n=27, spironolactone 25 mg). Subjects were followed over 12 weeks and baseline and 12-week serum potassium being compared. Other baseline base line laboratory investigation such as serum lipid profile, HbA1c, eGFR, fundus examination, ultrasonography (KUB), serum urea, serum creatinine, hemoglobin, were taken at the starting point.

**Results:** Both the group after receiving respective drug were followed for 3-month duration and serum potassium level measured at end of 3 months. Mean values of baseline and follow up serum potassium for group A and group B were 4.24±0.59, 4.07±0.61 and 4.35±0.55, 4.16±0.61 respectively, p value found to be >0.05 at 95% CI.

**Conclusions:** In the study it was concluded that p value found to be >0.05 at 95% C.I denoting that there is no significant difference between mean value of base line and follow up serum potassium value in both group. None of patients in either group had experienced hyperkalaemia over follow up period though serum potassium level were slightly higher in group A, but this difference was statistically not 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.

**Keywords:** Albumin creatinine ratio, Angiotensin converting enzyme, Estimated glomerular filtration rat, Glycated haemoglobin

### 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.<sup>1</sup>

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.<sup>2</sup>

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.<sup>3,4</sup>

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.<sup>5</sup> Adjuvant therapy with aldosterone receptor blockers such as spironolactone can be effective for the albuminuria improvement.<sup>6-9</sup>

Objective of this study was to evaluate the change in serum potassium level over follow up period in patients of diabetic nephropathy on spironolactone (25 mg) and ramipril (5 mg) and compare the results with diabetic nephropathy patients on Spironolactone (25 mg) alone.

## METHODS

Study was conducted on 64 patients (30-70 yr.) of diagnosed type 2 diabetes mellitus showing proteinuria (according to ADA). Total duration of study was about one year from October 2017 to October 2018. Patients after screening were selected for study and 32 patients were given Spironolactone (25 mg OD) along with Ramipril 5 mg and s 32 patients were given Spironolactone (25 mg OD) alone 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 64 patients out of which 9 patients did not come 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

- Age 30-70years,
- diagnosed type 2 diabetes mellitus,
- serum potassium level <5 meq/l,
- Estimated GFR >30 ml/min/1.73m<sup>2</sup> and HbA1c <10%.

### Exclusion criteria

- Type 1 diabetes mellitus,
- Impaired glucose tolerance secondary to endocrine disease,
- exocrine pancreatic disease, SBP>180 mmHg DBP >110 mmHg, ,
- UTI, hematuria,
- acute febrile illness,
- vigorous exercise,
- short-term pronounced hyperglycemia,
- obstructive uropathy,
- Confirmed or suspected renal artery disease by USG doppler study,
- Serum potassium level >5.5 meq/l,
- Congestive heart failure,
- Prior myocardial infarction, or stroke during preceding six month

- 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 the first 32 patients chronologically were given Spironolactone (25 mg OD) along with Ramipril 5 mg and subsequent 32 patients were given Spironolactone (25 mg 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. Other base line laboratory investigation such as serum lipid profile, HbA1c, eGFR, fundus examination, ultrasonography (KUB), serum urea, serum creatinine, hemoglobin, were taken at the starting point.

Base line serum potassium values for both the groups were compared at follow up serum potassium values at 12 weeks.

### Statistical analysis

Data obtained from the two study groups were compiled and tabulated and continuous variables are expressed as mean $\pm$ 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  $53.87\pm 9.51$  years. 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 A and subsequently enrolled 34 patients were allotted group B. The mean age of patient in Group A was  $55.37\pm 8.96$  compared to the mean age of patient in group B were  $52.46\pm 10.24$ . (Table 1 shows baseline characteristics of two groups.)

**Table 1: Baseline characteristics of two groups.**

| Variables                         | Group A (mean $\pm$ SD) | Group B (mean $\pm$ SD) | p value |
|-----------------------------------|-------------------------|-------------------------|---------|
| Age (years)                       | 55.37 $\pm$ 8.96        | 52.46 $\pm$ 10.24       | 0.25    |
| Hba1c (%)                         | 7.91 $\pm$ 1.34         | 8.31 $\pm$ 1.42         | 0.28    |
| S. urea (mg/dl)                   | 55.70 $\pm$ 25.98       | 78.78 $\pm$ 40.80       | 0.01    |
| S. creatinine(mg/dl)              | 1.50 $\pm$ 0.67         | 2.02 $\pm$ 1.07         | 0.03    |
| S. Tgl (mg/dl)                    | 163.33 $\pm$ 59.22      | 172 $\pm$ 75.54         | 0.63    |
| S. LDL (mg/dl)                    | 108.81 $\pm$ 85.01      | 92.35 $\pm$ 40.37       | 0.36    |
| S. HDL (mg/dl)                    | 49.42 $\pm$ 11.96       | 51.47 $\pm$ 18.19       | 0.62    |
| Blood sugar (mg)                  | 185.77 $\pm$ 58.11      | 184.35 $\pm$ 55.1       | 0.92    |
| eGFR (ml/min/1.73m <sup>2</sup> ) | 111.8 $\pm$ 22.5        | 110.5 $\pm$ 23.6        | 0.64    |
| Urine ACR                         | 471.5 $\pm$ 465.62      | 474.88 $\pm$ 438.94     | 0.97    |
| S. Potassium                      | 4.24 $\pm$ 0.59         | 4.07 $\pm$ 0.61         | 0.29    |

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. Both the group after receiving respective drug were followed for 3-month duration. Mean value of serum potassium at start of study for group A  $4.24\pm 0.59$ , as compared to mean

value of group B were  $4.07 \pm 0.61$ . p value found to be  $>0.05$  at 95% C. I, which denotes that there was no significant difference between value of base line serum potassium of both groups. (Table 2- showing Base line serum potassium value in group A and group B).

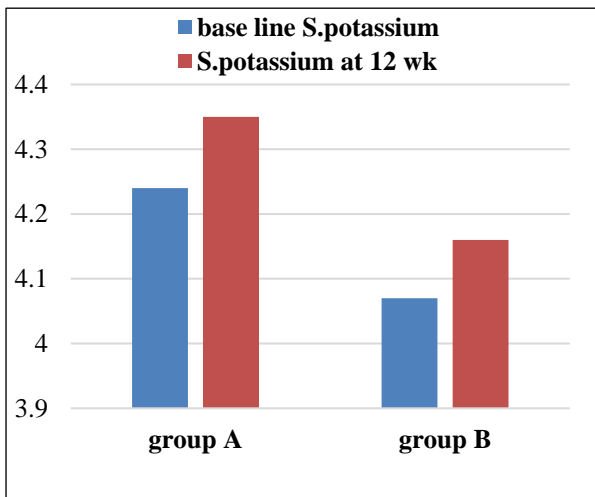
After follow-up period serum potassium mean value at 12week for group A  $4.35 \pm 0.55$ , as compared to group B  $4.16 \pm 0.61$ . p value found to be  $>0.05$  at 95% C. I, which denotes that there was no significant difference between value of follow up urine ACR of both groups. (Table 2 showing 12-week serum potassium value in group A and group B)

**Table 2: Base line and 12-week serum potassium mean value with SD in group A and group B.**

|                           | Group A         | Group B         | p value |
|---------------------------|-----------------|-----------------|---------|
| Base line serum potassium | $4.24 \pm 0.59$ | $4.07 \pm 0.61$ | 0.29    |
| Follow up serum potassium | $4.35 \pm 0.55$ | $4.16 \pm 0.61$ | 0.23    |

for base line serum potassium t cal=1.05, CI 95%, p value  $>0.05$   
for follow up serum potassium t cal = 1.21, C.I 95%, p value  $>0.05$

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



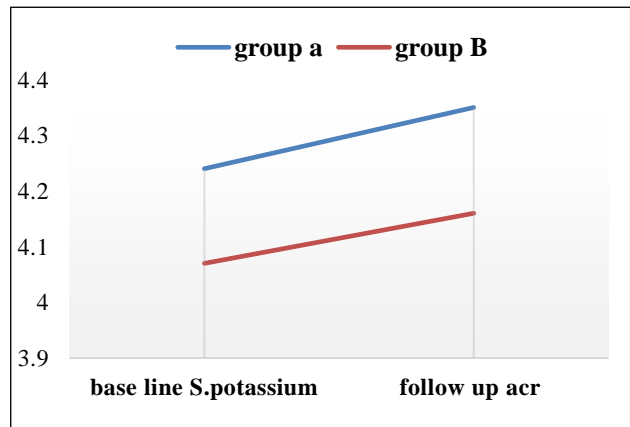
**Figure 1: Correlation between baseline and follow up serum potassium in both groups.**

For comparing effects within a group paired t test is applied separately in each group, t calculated was found less than value of t observed with p value  $>0.05$  which proved statistically not significant and denotes that there was no significant difference between base line and follow up serum potassium level in either group (Figure 2).

**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 C.I 95%), higher in group B patients. Both groups were then followed for next 12 weeks and serial changes in values of urine ACR and serum potassium were assessed.

Mean value of serum potassium at start of study for group A  $4.24 \pm 0.59$ , as compared to mean value of group B were  $4.07 \pm 0.61$ . p value found to be  $>0.05$  at 95% C.I, which denotes that there was no significant difference between value of base line serum potassium of both groups. After follow-up period serum potassium mean value at 12week for group A  $4.35 \pm 0.55$ , as compared to group B  $4.16 \pm 0.61$ . p value found to be  $>0.05$  at 95% C.I, which denotes that there was no significant difference between value of follow up urine ACR of both groups.



**Figure 2: The linear relation in the mean serum potassium values in subjects of group a and group b after 12 weeks follow up.**

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

For comparing effects within a group paired t test is applied separately in each group, t calculated was found less than value of t observed with p value  $>0.05$  which proved statistically not significant and denotes that there was no significant difference between base line and follow up serum potassium level in either group (Figure 2).

Similar results regarding safety of spironolactone with respect to occurrence of hyperkalemia were found by Rossing K, Christensen PK et al. After three months, successful treatment was seen in 70% (95% CI: 52-83) and 83.3% (CI 95%: 66-93) of case and control groups, respectively (p=0.4). Mean±SD of serum potassium levels after three months in case and control groups were

4.56±0.38 and 4.39±0.34 mEq/L, respectively (p=0.08), similar result was found in this study.<sup>10</sup>

Atieh Makhloogh, Zahra Kashi, et al, in study of spironolactone along with losartan in diabetic nephropathy observed that After three months, successful treatment was seen in 70% (95% CI: 52-83) and 83.3% (CI 95%: 66-93) of case and control groups, respectively (p=0.4). Mean±SD of serum potassium levels after three months in case and control groups were 4.56±0.38 and 4.39±0.34 mEq/L, respectively (p = 0.08).

Mean±SD of systolic blood pressures in case and control groups were 129.67±9.4 and 130.97±9.4 mmHg, respectively (p=0.6). Mean±SD of serum creatinine levels at the end of the study were 0.95±0.15 in case and 0.90±0.22 mg/dL in control group (p=0.4).<sup>11</sup>

## CONCLUSION

In the study p value was found to be >0.05 at 95% C.I denoting that there is no significant difference between mean value of base line and follow up serum potassium value in both groups. None of patients in either group had experienced hyperkalemia over follow up period though serum potassium level were slightly higher in group A, but this difference was statistically not significant. It can be concluded that low dose of spironolactone can be added over conventional ACEi therapy for proteinuria reduction in diabetic nephropathy patients without any significant hyperkalemia. Though Follow up period of study should be long enough to comment on safety profile of combining spironolactone and ACE inhibitors in diabetic nephropathy patients.

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