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Effect of Low-Dose Spironolactone on Proteinuria in Diabetic Kidney Disease — A Randomized Controlled Trial

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ABS TRAC T

***Background*:** Residual proteinuria persists in many diabetic kidney disease patients despite maximal renin-angiotensin-aldosterone system blockade with ACE inhibitors or angiotensin receptor blockers. Low-dose spironolactone has been proposed as an adjunctive anti-proteinuric agent targeting aldosterone-mediated renal injury. ***Methods*:** A double-blind placebo-controlled randomized trial was conducted from March 2022 to April 2023. Ninety-six patients with diabetic kidney disease and persistent proteinuria (urine protein-creatinine ratio above 0.5 g/g) despite maximal ACE inhibitor or ARB therapy for at least 3 months were randomized to receive spironolactone 25 mg daily (n equals 48) or matching placebo (n equals 48) for 24 weeks. The primary endpoint was percentage change in UPCR from baseline. Secondary endpoints included change in eGFR, blood pressure, and serum potassium. ***Results*:** Mean baseline UPCR was 1.82 plus or minus 0.86 in the spironolactone group and 1.78 plus or minus 0.92 g/g in the placebo group. At 24 weeks, spironolactone reduced UPCR by 34.2% versus 8.6% with placebo (p less than 0.001). Mean absolute UPCR reduction was 0.62 plus or minus 0.38 versus 0.16 plus or minus 0.24 g/g (p less than 0.001). eGFR remained stable in both groups (change minus 1.2 versus minus 2.4 mL/min, p equals 0.286). Systolic BP decreased more with spironolactone (minus 8.4 versus minus 3.2 mmHg, p equals 0.006). Hyperkalaemia above 5.5 mEq/L occurred in 12.5% versus 2.1% (p equals 0.048) but none exceeded 6.0 mEq/L or required discontinuation. ***Conclusion*:** Low-dose spironolactone at 25 mg daily significantly reduced proteinuria by 34% in diabetic kidney disease patients with residual proteinuria on maximal RAAS blockade. The treatment was well-tolerated with manageable hyperkalaemia risk. Regular potassium monitoring is recommended.

Keywords: *Spironolactone, Proteinuria, Diabetic Kidney Disease, Mineralocorticoid Receptor Antagonist, Randomized Controlled Trial.*

INTRODUCTION

Diabetic kidney disease is the leading cause of end-stage renal disease in both developed and developing countries [1]. Despite optimal therapy with renin-angiotensin-aldosterone system blockade using angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, a substantial proportion of patients continue to exhibit clinically significant proteinuria and progressive renal decline [2]. This residual risk has been attributed in part to the phenomenon of aldosterone breakthrough, wherein aldosterone levels rise despite ACE inhibitor or ARB therapy in up to 40% of patients after 6 to 12 months of treatment [3].

Aldosterone exerts direct deleterious effects on the kidney independent of its classical effects on sodium and potassium homeostasis. These include promotion of renal inflammation, fibrosis, oxidative stress, and podocyte injury through activation of mineralocorticoid receptors in mesangial cells, podocytes, and tubular epithelial cells [4]. Experimental studies in rodent models of diabetic nephropathy have demonstrated that mineralocorticoid receptor blockade reduces proteinuria, attenuates glomerulosclerosis, and diminishes tubulointerstitial fibrosis beyond the effects of RAAS blockade alone [5].

Spironolactone, a non-selective mineralocorticoid receptor antagonist, has shown promise as an adjunctive anti-proteinuric agent in

several small clinical trials. A meta-analysis of eight randomized controlled trials involving 459 patients demonstrated that the addition of an MRA to ACE inhibitor or ARB therapy reduced proteinuria by approximately 35 to 40% compared to RAAS blockade alone [6]. However, concerns regarding hyperkalaemia have limited the widespread adoption of this approach, particularly in patients with impaired renal function [7].

The safety and efficacy data for spironolactone add-on therapy in diabetic kidney disease are derived predominantly from Western and East Asian populations. Data from Southeast Asian populations, where the prevalence of diabetic kidney disease is rapidly increasing, remain limited [8]. The threshold for potassium-related adverse effects may differ across populations due to variations in dietary potassium intake, body composition, and concomitant medication use [9].

The present study was undertaken as a randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of low-dose spironolactone as add-on therapy to maximal RAAS blockade in Indonesian patients with diabetic kidney disease and persistent proteinuria [10].

AIMS AND OBJECTIVES

The present randomized controlled trial was undertaken to evaluate the efficacy of low-dose spironolactone 25 mg daily added to maximal ACE inhibitor or ARB therapy in reducing proteinuria in patients with diabetic kidney disease and persistent proteinuria, to assess the effect on eGFR and blood pressure, and to determine the safety profile with particular attention to hyperkalaemia risk over a 24-week treatment period.

MATERIALS AND METHODS

Study Design and Setting

This was a prospective, randomized, double-blind, placebo-controlled, parallel-group trial conducted from March 2022 to April 2023 at the Department of Nephrology, University Teaching Hospital, Jakarta, Indonesia. The study was approved by the Institutional Ethics Committee and registered with the national clinical trials registry. All patients provided written informed consent.

Sample Size

Ninety-six patients were enrolled. Sample size was calculated to detect a 25% difference in UPCR reduction between groups with standard deviation of 0.4, two-sided alpha of 0.05, and power of 80%, requiring 42 patients per group, increased to 48 to allow for 12% attrition.

Inclusion Criteria

Adults aged 18 to 70 years with type 2 diabetes mellitus and diabetic kidney disease with persistent proteinuria defined as UPCR above 0.5 g/g on two consecutive measurements despite maximal tolerated dose of ACE inhibitor or ARB for at least 3 months, eGFR between 30 and 90 mL/min/1.73 m squared, and serum potassium below 5.0 mEq/L at screening were included.

Exclusion Criteria

Patients with serum potassium above 5.0 mEq/L, eGFR below 30, non-diabetic kidney disease, current use of potassium-sparing diuretics or potassium supplements, NYHA class III to IV heart failure, known allergy to spironolactone, pregnancy or breastfeeding, and those unable to attend follow-up visits were excluded.

Procedure and Data Collection

Randomization was performed using computer-generated random numbers in blocks of 4 with allocation concealment using sequentially numbered, opaque sealed envelopes. The spironolactone and placebo tablets were identical in appearance, size, and packaging. Patients received either spironolactone 25 mg once daily or matching placebo for 24 weeks. All patients continued their existing ACE inhibitor or ARB at maximal tolerated dose. Other medications including antidiabetic agents, statins, and non-RAAS antihypertensives were continued unchanged unless clinically indicated. Laboratory measurements at each visit included serum creatinine, eGFR, serum potassium, sodium, blood urea nitrogen, spot UPCR, and blood pressure. If serum potassium exceeded 5.5 mEq/L, the study drug was halved to every other day; if it exceeded 6.0 mEq/L, the drug was discontinued.

Follow-Up Protocol

Follow-up visits were scheduled at 4, 8, 12, 16, 20, and 24 weeks. At each visit, blood pressure, serum potassium, serum creatinine, and spot UPCR were measured. Twenty-four-hour urine protein was collected at baseline, 12, and 24 weeks. Patients were instructed to maintain a consistent dietary pattern and to avoid excessive potassium-rich foods. Adverse events were recorded at each visit.

Statistical Analysis

Data were analysed on an intention-to-treat basis using SPSS version 13.0. The primary outcome (percentage change in UPCR at 24 weeks) was compared using Student t-test for independent samples. Within-group changes were assessed using the paired t-test. Repeated measures ANOVA was used for longitudinal analysis. Categorical variables were compared using chi-square test. A responder analysis was performed defining response as UPCR reduction of 30% or more. Number needed to treat was calculated. p less than 0.05 was considered significant.

RESULTS

Ninety-six patients were randomized (48 per

group) and 88 completed the 24-week follow-up (44 spironolactone, 44 placebo; attrition 8.3%). Baseline characteristics were comparable between groups. Mean age was 54.8 plus or minus 9.6 versus 55.2 plus or minus 10.2 years. Mean diabetes duration was 10.8 plus or minus 5.4 versus 11.2 plus or minus 5.8 years. Baseline UPCR was 1.82 plus or minus 0.86 versus 1.78 plus or minus 0.92 g/g. Baseline eGFR was 52.4 plus or minus 16.8 versus 54.2 plus or minus 18.2 mL/min.

At 24 weeks, the spironolactone group showed a mean UPCR reduction of 34.2% versus 8.6% in the placebo group (between-group difference 25.6%, 95% CI 18.4 to 32.8, p less than 0.001). The mean absolute UPCR decreased from 1.82 to 1.20 g/g in the spironolactone group versus 1.78 to 1.62 g/g in the placebo group. The proteinuria reduction was apparent by 8 weeks and plateaued by 16 weeks.

Respazonder analysis showed that 64.6% in the spironolactone group achieved a UPCR reduction of 30% or more compared with 18.8% in the placebo group (p less than 0.001; NNT equals 2.2). eGFR change was minus 1.2 plus or minus 3.4 in the spironolactone group versus minus 2.4 plus or minus 3.8 in placebo (p equals 0.286). SBP decreased by 8.4 plus or minus 6.2 mmHg versus 3.2 plus or minus 4.8 mmHg (p equals 0.006).

Hyperkalaemia (potassium above 5.5 mEq/L) occurred in 6 spironolactone patients (12.5%) versus 1 placebo patient (2.1%, p equals 0.048). In all 6 spironolactone cases, potassium ranged between 5.5 and 5.9 mEq/L, and resolved with dose reduction to alternate-day dosing in 4 and dietary modification in 2. No patient exceeded 6.0 mEq/L or required discontinuation. Gynaecomastia or breast tenderness occurred in 2 spironolactone patients (4.2%) but did not lead to withdrawal.

Table 1: Baseline Characteristics

Parameter	Spironolactone (n=48)	Placebo (n=48)	p-value
Age (years)	54.8 +/- 9.6	55.2 +/- 10.2	0.842
Male, n (%)	28 (58.3%)	30 (62.5%)	0.674
DM duration (years)	10.8 +/- 5.4	11.2 +/- 5.8	0.724
UPCR (g/g)	1.82 +/- 0.86	1.78 +/- 0.92	0.816
eGFR (mL/min)	52.4 +/- 16.8	54.2 +/- 18.2	0.608
HbA1c (%)	7.8 +/- 1.4	7.6 +/- 1.2	0.446
SBP (mmHg)	142.6 +/- 14.8	140.8 +/- 16.2	0.562
K+ (mEq/L)	4.4 +/- 0.4	4.3 +/- 0.4	0.226
On ACEi, n (%)	32 (66.7%)	30 (62.5%)	0.672
On ARB, n (%)	16 (33.3%)	18 (37.5%)	0.672

Table 2: Primary Outcome — UPCR Changes at 24 Weeks

Parameter	Spironolactone	Placebo	p-value
Baseline UPCR (g/g)	1.82 +/- 0.86	1.78 +/- 0.92	0.816
24-week UPCR (g/g)	1.20 +/- 0.64	1.62 +/- 0.84	0.006
Absolute change	−0.62 +/- 0.38	−0.16 +/- 0.24	<0.001
% change	−34.2%	−8.6%	<0.001
Responders (>=30% reduction)	31 (64.6%)	9 (18.8%)	<0.001
NNT	2.2	—	—

Table 3: Secondary Outcomes at 24 Weeks

Parameter	Spironolactone	Placebo	p-value
eGFR change (mL/min)	−1.2 +/- 3.4	−2.4 +/- 3.8	0.286
SBP change (mmHg)	−8.4 +/- 6.2	−3.2 +/- 4.8	0.006
DBP change (mmHg)	−4.2 +/- 3.8	−1.8 +/- 3.4	0.012
HbA1c change (%)	−0.2 +/- 0.4	−0.1 +/- 0.4	0.268
K+ change (mEq/L)	+0.3 +/- 0.3	+0.04 +/- 0.2	<0.001

Table 4: Time Course of UPCR Reduction (Spironolactone Group)

Timepoint	UPCR (g/g)	% Change from Baseline	p vs Baseline
Baseline	1.82 +/- 0.86	—	—
8 weeks	1.42 +/- 0.72	−22.0%	<0.001
16 weeks	1.24 +/- 0.66	−31.9%	<0.001
24 weeks	1.20 +/- 0.64	−34.2%	<0.001

Table 5: Safety — Adverse Events

Event	Spironolactone n (%)	Placebo n (%)	p-value
K+ > 5.5 mEq/L	6 (12.5%)	1 (2.1%)	0.048
K+ > 6.0 mEq/L	0 (0%)	0 (0%)	—
Drug dose reduction	4 (8.3%)	0 (0%)	0.042
Gynaecomastia	2 (4.2%)	0 (0%)	0.153
Dizziness	3 (6.3%)	2 (4.2%)	0.646
GI upset	2 (4.2%)	1 (2.1%)	0.558
Study discontinuation	4 (8.3%)	4 (8.3%)	1.000

DISCUSSION

The 34.2% reduction in proteinuria observed with spironolactone is consistent with the 30 to 40% range reported in the meta-analysis by Bolignano *et al*., [11]. Chrysostomou and Becker [12] first demonstrated a 54% reduction in proteinuria with spironolactone 25 mg added to ACE inhibitor therapy in a smaller cohort of 41 patients. The somewhat lower reduction in the present study may reflect the inclusion of patients with higher baseline proteinuria and more advanced disease.

The anti-proteinuric effect was evident by 8 weeks and plateaued by 16 weeks, consistent with the findings of Bianchi *et al*., [13] who reported maximal proteinuria reduction at 12 to 16 weeks. This temporal pattern likely reflects the time course of mineralocorticoid receptor-mediated podocyte recovery and reduction in glomerular permeability.

The preservation of eGFR in the spironolactone group is reassuring and consistent with the initial reversible GFR dip phenomenon observed with RAAS blockade. Mehdi *et al*., [14] similarly reported stable eGFR over 48 weeks of spironolactone therapy in diabetic nephropathy patients.

The hyperkalaemia rate of 12.5% is comparable to the 10 to 15% reported in most trials of MRA add-on therapy. Edwards *et al*., [15] reported potassium above 5.5 in 11.8% of patients on eplerenone add-on. Importantly, no patient exceeded 6.0 mEq/L, and all cases were manageable with dose adjustment or dietary modification. This supports the safety of low-dose spironolactone with appropriate monitoring [16].

The additional blood pressure reduction of 5.2 mmHg is clinically relevant, as each 5 mmHg SBP reduction has been associated with approximately 10% reduction in cardiovascular events [17]. This haemodynamic benefit likely contributes to the anti-proteinuric effect.

The high responder rate (64.6% vs 18.8%, NNT 2.2) suggests that spironolactone add-on provides clinically meaningful benefit in a substantial proportion of patients. Furumatsu *et al*., [18] reported similar response rates in Japanese patients. The non-responders may represent patients without significant aldosterone breakthrough or those with predominantly non-haemodynamic mechanisms of proteinuria [19].

Limitations include the 24-week duration (long-term safety and renal outcomes are unknown), single-centre design, and the small sample size which limits power for subgroup analyses. Future studies should evaluate hard renal endpoints [20].

CONCLUSION

Low-dose spironolactone at 25 mg daily significantly reduced proteinuria by 34.2% in diabetic kidney disease patients with persistent proteinuria despite maximal RAAS blockade, compared to 8.6% with placebo. The treatment was well-tolerated, with manageable hyperkalaemia in 12.5% of patients, none requiring drug discontinuation. eGFR remained stable and additional blood pressure reduction was observed. These findings support the use of low-dose spironolactone as adjunctive therapy in diabetic kidney disease with residual proteinuria. Regular serum potassium monitoring at 4-week intervals for the first 12 weeks and periodically thereafter is recommended.

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