The Effects of Adding Spironolactone to ACEI or ARB on Proteinuria in Type 2 Diabetes

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Abstract

Objectives: Interruption of rennin-angiotensin-aldosterone system has become a leading therapeutic strategy in the treatment of diabetic nephropathy; however, ACEIs and ARBs do not uniformly suppress the rennin-angiotensin-aldosterone system. Plasma aldosterone levels are elevated in a group of patients despite therapy and this phenomenon known as aldosterone escape or aldosterone break through.

Materials and Methods: Forty-two type 2 diabetic patients with overt proteinuria were randomized into two groups and according to double-blind case-control study, one group was treated with spironolactone and others were treated with placebo for 4 months. Twenty-four hours urine protein, glomerular filtration rate (GFR) and blood pressure were measured at baseline and after 4 months of treatment. Serum potassium was checked at baseline and one month of treatment.

Results: Urine protein decreased in case group by 26.5% at the end of 4 months, but increased in control group by 17.9% (P=0.003). GFR did not have any significant change in case group (P<0.354), but decreased in case group significantly (P<0.001).

Conclusion: Our study showed that spironolactone 12.5 mg/day is safe (without hyperkalemia and gynecomastia) and effective to decrease proteinuria in diabetic patient with CKD1-2.

Keywords: Diabetic nephropathy, Aldosterone, Spironolactone, Aldosterone escape, Chronic kidney disease.

Introduction

Diabetes is an increasing concerning health problem in the world (1,2). The increased prevalence of diabetes is related to rapid economic development, improved living standards, an aging population, a westernized life style, obesity and decreased physical activity, and short sleep duration (2).

Diabetic nephropathy is a microvascular complication of diabetes and is the main cause of end-stage renal disease (ESRD) in United States and a leading concern of morbidity and mortality in diabetic patients (3-9). Proteinuria is a well-defined risk factor for progression of CKD and cardiovascular disorder in diabetes (10-16).

For several decades, suppression of the renin-angiotensin-aldosterone system (RAAS) by

angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs), has been a focus for renoprotection (17).

In clinical trials of ACEIs and ARBs, plasma aldosterone levels, after an initial decline, have been shown to increase in some patients over the long term. This phenomenon is termed "aldosterone escape" or "aldosterone break through"; the incidence of this phenomenon ranged from 10% over 6 months to 53% over 1 year (18). Aldosterone break through occurs in 20% of patients with CHF and 40% of diabetic nephropathy (19). Aldosterone break through is due to cleaving angiotensin I to angiotensin II by non-ACE enzymes, hyperkalemia, AT2-receptor dependent mechanism, and an increase in ANP levels during ARB or ACEI therapy (20).

There is increasing clinical evidence that aldosterone blockade with mineralocorticoid receptor blockers have strong antiproteinuric effects (19,21). Aldosterone may have an independent role in renal fibrosis through TGF-B signaling pathways which upregulate collagen synthesis, downregulate the release of the extracellular matrix metalloproteinase collagenase, and promote fibroblasts proliferation. Aldosterone involves in ROS production in proximal tubular cells and leads to cell apoptosis, and also increases connective tissue growth factor (CTGF) gene and protein synthesis that is a TGF-B independent pathway. Aldosterone induces renal expression of proinflammatory cytoxins: osteopontins, membrane cofactor protein 1, IL-6 and IL-18; it promotes fibroblast growth and proliferation, and induce renal injury at least in part by enhancing PAI-1 expression; which tips the balance in favor of extracellular matrix accumulation, and eventually promoting renal fibrosis (22).

Recent evidence also indicated that aldosterone inhibition may have additional renoprotective effect in diabetic patients especially who experience aldosterone escape phenomenon due to ACEIs treatment (17,19). Spironolactone prevents diabetic nephropathy through reduction of CTGF synthesis in type 2 diabetic rats (23).

Recent studies show that glomerular podocyte abnormalities (including functional changes and loss) are features of diabetic nephropathy (24,25). In subtotally nephrectomized rats, mineralocortical blockade provided additional renoprotection over the ACEI. Such benefit was paralleled by changes in podocyte number and morphology and independent of BP (26). Therefore, we have provided a double-blind randomized controlled trial study to show the supplemental effect of spironolactone on proteinuria in type 2 diabetic patients.

Materials and Methods

Between April 2012 and February 2013, we consecutively enrolled 42 type 2 diabetic patients with nephropathy (proteinuria>300mg/ 24-hr), who were receiving an ACEI and or ARB for more than one year. The patients entered the study according to inclusion criteria (GFR>60ml/min, BMI<30 kg/m^2 and HbA1c<8.5%). We excluded patient with BP<100/60 mmHg or BP>150/90 mmHg and serum k>5 mg/dl.

The study protocol was approved by the ethics committee of our institution; and informed consent was obtained from the patients. This study was a double-blind case-control trial and for ensuring that randomization is tamper proof, we set up a separate randomized facility that the trial staff was contacted by telephone when an eligible participant was ready to be randomized. The staff member was provided the name and study number of the new participant. This information was recorded and the treatment group was then randomly assigned (according to computer programs). Therefore the patients were randomly managed with placebo or spironolactone 12.5 mg/day. Demographic data, BP, BMI, serum potassium, serum creatinine, HbA1c, GFR and 24-hr urine protein were evaluated at baseline. Serum k was checked again after one month; also, BP, serum k, serum creatinine, HbA1c, GFR and 24-hr urine protein were checked

after 4 months again.

We measured GFR according to MDRD formula. FBS was measured by standard method, serum k was measured by Ione selective (ElectroAnalyzer-XD648-Madmehr company) and serum creatinine concentration was assessed by Jafee (Bionic,Farasamed company). 24-hr urine collection was done for measurement of protein and creatinine. Urine protein measurement was made by Esleba solution. HbA1c was measured by HPLC (Adams HA 8160, Arcray Company, Japan).

Statistical Analysis

Statistical analysis was performed by using statistical package for social sciences (SPSS, version 17). Almost all data expressed as mean±SD. Categorical data were compared by means of chi-square test and continuous variables by means of student t-test. We used Mann-Whitney test to evaluate the changes in urine protein before and after intervention in two study groups. Statistical significance was defined as p-value less than 0.05.

Results

A total of 42 patients were enrolled in this study. Baseline characteristics, demographic, laboratory parameters and medication used in our study patients are listed in Table 1. There were no statistically significant differences between the two groups in terms of demographic data, blood pressure, GFR, serum creatinine, serum k, 24-hour urine protein using T-test). As presented in Table 2, there was no difference between the two groups for prescription of losartan, captopril and enalapril; but diltiazem was prescribed more in control group (chi-square test and Fisher's exact test) (*P*-value=0.019)

At the end of the study, urine protein decreased in spironolactone group by 26.5%, but increased in control group by 17.9%, (*P*=0.003, Figures 1,2).

GFR showed no significant changes in case group (*P*=0.35), but decreased in case group

Table1. Baseline characteristics of subjects in control and spironolactone group.

Characteristics	Control group	Spironolactone group	*P*-value
Age (years)	55.76±10.97	57.19±12.78	0.36
BMI (kg/m^2)	28.07±1.57	28.29±1.67	0.65
Blood pressure (mmHg)			
Systolic	134.77±10.17	142.23±12.58	0.55
Diastolic	81.50±9.03	82.00±7.18	0.36
HbA1c (%)	7.37±0.82	7.61±0.82	0.88
GFR (ml/min/1/73m^2)	78.60±12.89	72.9±12.40	0.89
Serum creatinine (mg/ml)	0.99±0.148	1.07±0.173	0.14
Serum potassium (meq/l)	4.64±0.485	4.71±0.444	0.41
24-hr urine protein (mg)	968.09±761.24	1158.90±1534.23	0.20

Table 2. Comparison of the drugs used for the study groups.

Medication	Control group	Spironolactone group	*P*-value
ACEIs			
Enalapril	13 (61.9)	11 (52.8)	0.37
Captopril	5 (23.8)	1 (4.8)	0.09
ARBs			
Losartan	18 (85.7)	20 (95.2)	0.30
Valsartan	2 (9.5)	1 (4.8)	0.50
Calcium channel blocker			
Diltiazem	18 (85.7)	11 (52.4)	0.02

Data are presented as n (%).

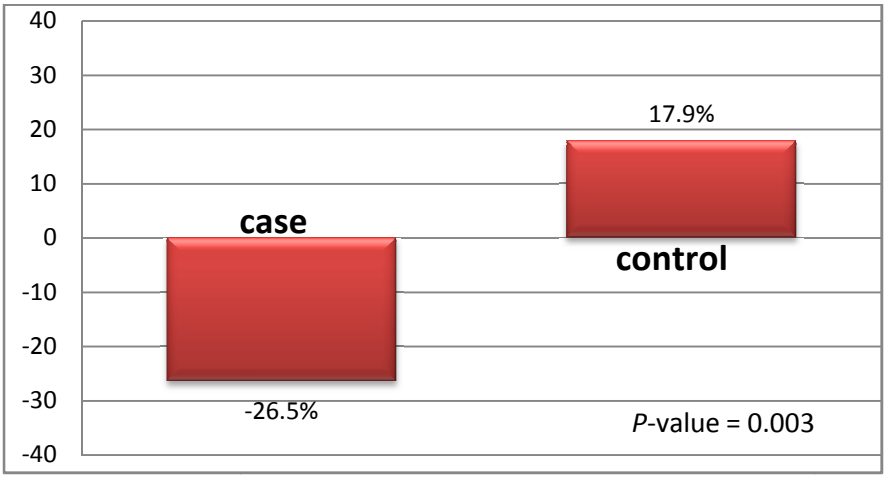

Figure1. 24-hr urine protein changes in tow groups before and after intervention.

significantly (*P*<0.001, Figure 3).

Changes in serum potassium, diastolic BP and systolic BP were not significant at the end of study in two groups Figures 4-6.

At the end of study, the mean HbA1c in case and control groups was 7.52±0.82 and 7.28±0.80, respectively, with no significant differences between the two groups (*P*-value=0.97).

Discussion

In this study we showed that treatment with 12.5 mg/day of spironolactone resulted in a 26.5% decrease in urine protein.

In other studies, with use of 25 mg/day of spironolactone, urine protein decreased by 33%, 30%, 15%, 38% and 20%, respectively (27-31). Only in Nowicki study, 12.5mg/day of spironolactone (similar to us) for 4 weeks resulted a decrease in urine protein by 38% (32).

Saklayen et al. did not find any change in serum k with use of spironolactone in diabetic patients, which was in accordance with our findings (33). Also, a systematic review showed that the risk of mineralocorticoid receptor blockade (MRB) –associated hyperkalemia can be minimized if this intervention is reserved for patient with GFR

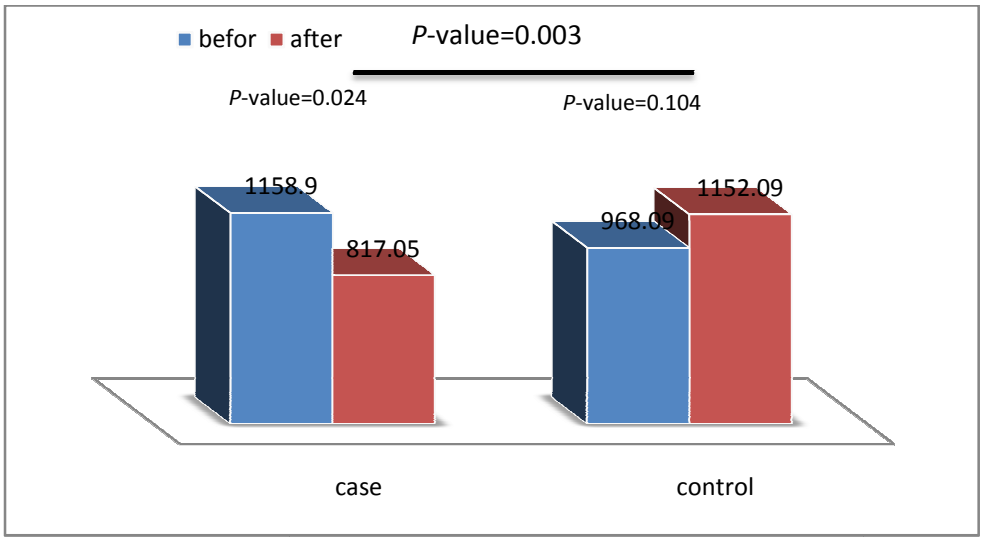

Figure 2. 24-hr urine protein in the two groups before and after intervention. Data are presented as mg/24hr.

greater than 60 ml/min/1.73m^2 (34).
In Saklayen study (33), GFR decreased after intervention with spironolactone (*P*=0.0001) while in our study, GFR decreased in control group (*P*=0.001). In a systematic review, MRB therapy (25-50mg/day) was associated with statistically significant decreased GFR in approximately 25% of included studies (34). We did not find any significant changes on systolic or diastolic BPs. Therefore, the effect of spironolactone is independent of decrease in BP. During the study we did not have any gynecomastia in the case group. According to these, it sounds that spironolactone with a dose of 12.5 mg/day is safe and effective.

Conclusion

Our study showed that spironolactone 12.5mg/day is safe (without hyperkalemia and gynecomastia) and effective to decrease proteinuria in diabetic patients with CKD1-2. This effect is independent of BP, and can protect GFR. We suggest a large RCT with this dose of spironolactone on CKD 3 and 4.

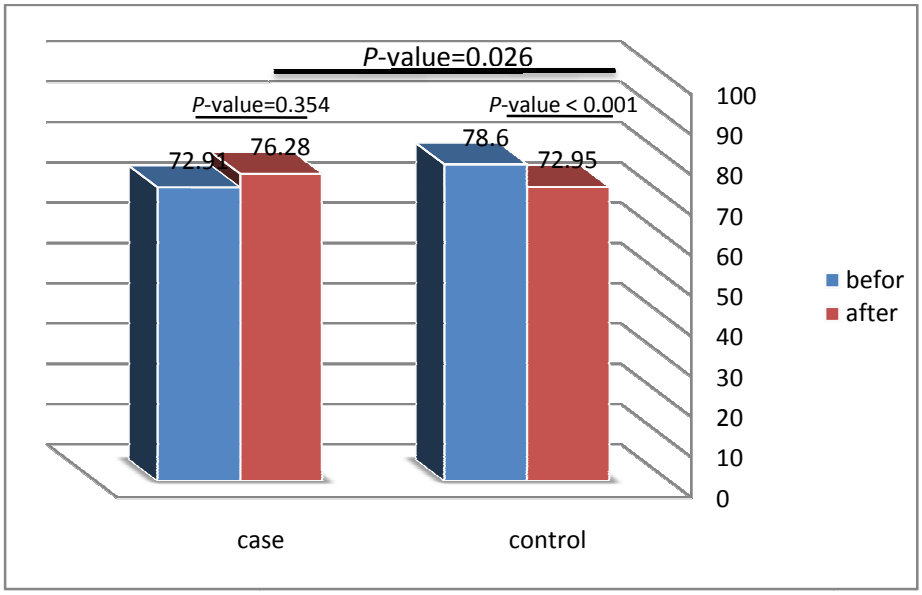

Figure 3. Glomerular Filtration Rate in the two groups before and after intervention. Data are presented as ml/min/1.73m^2.

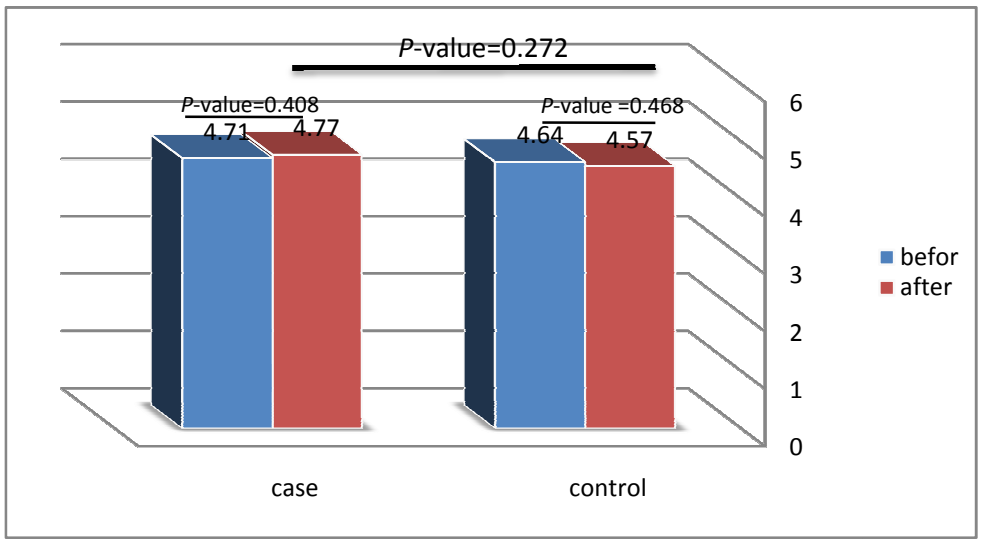

Figure 4. Serum potassium in two groups before and after intervention. Data are presented as meq/l.

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