Original Article

Effects of additive therapy with spironolactone on albuminuria in diabetes mellitus: A pilot randomized clinical trial

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Abstract

Background: Early diagnosis of albuminuria and the prevention of its progression to macroalbuminuria and diabetic nephropathy are crucial. Angiotensin converting enzyme inhibitors (ACEIs) and antagonists of angiotensin II receptors type I (ARBs) are currently used as first-line treatment for albuminuria in these patients. The present study was conducted to assess the efficacy of addition of spironolactone to ACEIs or ARB in the prevention of diabetic nephropathy.

Methods: Sixty patients were selected from the patients who referred to a Diabetes Clinic in this randomized clinical trial study. The control group received enalapril and the case group took additive therapy with spironolactone for 12 weeks. Blood pressure, concentrations of creatinine and albumin in the serum and urine, urinary albumin/creatinine ratio, serum potassium were determined for each patient in the beginning of and every 4-6 weeks until the end of the study. This clinical trial was registered in the Iranian Registry of Clinical Trials (www.irct.ir) with registration number ID: IRCT201105084849N2.

Results: There was statistically significant difference in albumin/creatinine ratio between the two groups ($p<0.001$). Albuminuria reduced more significantly in case group compared to control group. It was measured 66.6±26.8 mg/mmol and 45.7±19 mg/mmol in control and case groups, respectively. The patients did not develop any significant adverse effect including reduction in GFR, hyperkalemia, and hypotension.

Conclusion: Low to moderate doses of spironolactone can augment the effect of ACEIs in the prevention of diabetic nephropathy.

Keywords: Diabetic nephropathy, Albuminuria, Spironolactone, Angiotensin Converting Enzyme Inhibitors (ACEIs)

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Diabetes mellitus (DM) is a common metabolic disease. It is quite common in Iran, too. Its prevalence has been 6.1% in females and 8% in males in 2010 and it has been reported by the International Diabetes Federation. The prevalence of DM in Iran is higher than its northern nearby countries, for instance Armenia, Azerbaijan, Turkmenistan, and Russia (1). Diabetic nephropathy is one of the main causes of morbidity and mortality among the diabetics. The emergence of albuminuria in diabetic patients denotes progression of the disease and is associated with higher risk of cardiovascular complications (2, 3). Diabetic nephropathy is the most common cause of chronic renal failure (3-5). It is not clearly known how prolonged hyperglycemia can involve renal cells. However, it is suggested that some intermediary factors (include growth factors, angiotensin and endothelin), hemodynamic changes in capillary circulation (increase in circulation or glomerular filtration and increase in glomerular capillary pressure), and structural changes in glomerules (glomerular cells hypertrophy, and increase in external matrix or growth factors), and inflammation processes may contribute this effect (6).

Angiotensin converting enzyme inhibitors (ACEI) and antagonists of angiotensin II receptors type I (ARB) may diminish proteinuria and help to reduce the rate of glomerulosclerosis (7-14). Nonetheless, several studies have reported that ACEIs or ARBs decrease serum aldosterone concentration through the inhibition of the renin angiotensin – aldosterone system (RAS) only for the short term and its level returns towards normal or near normal after some time. This phenomenon is referred as aldosterone escape phenomena (15, 16). The national Kidney Foundation (KDOQI) has advised ACEIs and ARBs as first-line treatment for diabetic patients with nephropathy. The drugs can lower intraglomerular and intraarterial pressure by means of inhibition of the RAS and in this way, they can hinder progression of the disease to chronic renal failure (17). There are a number of studies that have claimed that spironolactone can potentiate the effect of ACEIs and ARBs in the prevention of diabetic nephropathy with promising results (2, 4, 18).

The present study aimed to evaluate the effect of enalapril alone and with spironolactone in the prevention of diabetic nephropathy among Iranian diabetics.

Methods

In this pilot clinical trial study, the patients were selected from the Diabetes Clinic in a university teaching hospital in Qazvin, Iran from December 2010 to September 2011. The patients were assigned to case and control groups by random allocation. The control group received daily enalapril 25 mg PO Bid for 12 weeks.

The study group took spironolactone 25 mg PO daily for 12 weeks, besides daily enalapril 25 mg PO Bid for 12 weeks. Informed consent was taken from all the patients. The study was approved by the local Ethics Committee of Qazvin University of Medical Sciences.

Sixty patients aged 18-80 years old were selected if they had the inclusion criteria. The inclusion criteria were microalbuminuria after diabetic nephropathy (DM type II) confirmed with 24-hours urine sample, the age between 18-80 years, and at least 3 months treatment with ACEIs prior to the present study. Any patient with serum creatinine more than 2 mg/dl, serum potassium more than 5.5 mmol/dl, cardiac ejection fraction less than 35%, systolic blood pressure less than 90 mmHg or symptomatic hypotension, and any contraindication for prescription of the selected drugs was excluded from the study.

Blood pressure, concentrations of creatinine and albumin in the serum and urine, urinary albumin/creatinine ratio, serum potassium concentration were determined for each patient in the beginning, and every 4-6 weeks until the end of the study. The blood pressure was measured in a controlled standard condition. The laboratory measurements were performed in the clinical laboratory of Buali Hospital, a university teaching hospital with standard conventional methods.

Statistical analysis: The **c**omparisons of quantitative and qualitative variables are calculated by mean±SD and percent between the two groups respectively and data was analyzed by a univariate test of repeated measures MANOVA to evaluate effect treatment.

Results

Twenty nine and 31 patients were enrolled in the case and control groups, respectively. The patients were 45-63 years old and their mean age was 53.07±5.05 years. The comparison between the main characteristics of case and control groups was demonstrated in table 1.

Table 1. Comparison between main characteristics of case and control groups

Variables	Control (n=31) Mean±SD	Case (n=29) Mean±SD
Disease duration	11.16±2.84	11.15±2.94
age	53.03±5.25	53.10±4.93
Glomerular Filtration Rate	82.55±19.18	79.84±18.05
Systolic blood pressure	124.19±12.85	127.24±12.50
diastolic blood pressure	75.96±8.60	79.31±8.42
serum creatinine	1.03±0.20	1.05±0.21
serum potassium	4.04±0.30	4.11±0.23
albumin/creatinine ratio	119±66.86	126.3±69.36

Thirty seven patients including 17 (66.5%) in case and 20 (64.5%) in control group were males (table 2). There was statistically significant difference in albumin/creatinine ratio between the groups, as it has been shown in table 3. Systolic and diastolic blood pressure and serum potassium concentration did not notably differ between the groups (table 4).

Table 2. Frequency of subjects' age based on gender

Gender Category	Females N (%)	Males N (%)	SUM N (%)
1-5	0 (0)	0 (0)	0 (0)
6-10	9 (15.3)	20 (34)	29 (48.3)
11-15	12 (20.4)	16 (27.2)	28 (47.6)
16-20	2 (3.4)	1 (1.7)	3 (5.1)
Total	23 (39.1)	37 (62.9)	60 (100)

Table 3. Comparison of albumin/creatinine and creatinine and GFR in the intervention and control groups

Group	before Mean±SD	after Mean±SD	F	Pvalue
albumin/creatinine				
Intervention	126±69.3	59.3±48.1	12.29	0.001
Control	119±66.8	73.2±53.3		
Creatinine				
Intervention	1.058±0.21	1.086±0.2	0.26	0.6
Control	1.034±0.2	1.051±0.1		
GFR				
Intervention	79.8±18	75.6±16.3	0.47	0.49
Control	82.5±19.1	79.6±16.6		

Table 4. Comparison of systolic blood pressure, diastolic blood pressure and potassium in the intervention and control groups at the beginning, middle and end of the study

Group	before Mean±SD	End of the sixth week Mean±SD	after Mean±SD	F	Pvalue
Systolic blood pressure					
Intervention	127.2±2.3	121.3±1.7	117.2±1.5	3.9	0.02
Control	124.1±2.2	118.5±1.6	118.2±1.5		
Diastolic blood pressure					
Intervention	79.3±1.5	71.3±0.8	70.6±0.68	2.34	0.1
Control	75.9±1.5	7.06±0.86	70.1±0.88		
Potassium					
Intervention	4.11±0.23	4.35±0.46	4.40±0.46	2.7	0.07
Control	4.04±0.30	4.16±0.26	4.16±0.25		

Discussion

The current study confirmed that the addition of spironolactone to enalapril can boost the effect of the latter on the decline of albumin/creatinine ratio i.e. severity of albuminuria and progression of diabetic nephropathy. Albumin/creatinine ratio reduced 66.6±29.6 from the start of the study to its end in case group at the same time the

reduction was 45.7±19 in control group. No relationship was found between the rate of albuminuria and age, gender, duration of the disease, and race of the patients. The general characteristics of the patients were comparable to the studies of Davidson and Rossing (2, 4).

Davidson et al. have verified that an addition of 25 mg spironolactone orally to ACEIs for 1 month improves microalbuminuria 27.2% and microalbuminuria 24.3% in DM type II (2). Schjoedt et al. have assessed the effects of addition of spironolactone to maximum permissible doses of ACEIs and ARBs in a double-blinded clinical trial on 21 diabetic patients. They have concluded that spironolactone reduces 33% of albuminuria in case group (4). Saklayen et al. have studied the effect of spironolactone on proteinuria in patients with diabetic nephropathy. They have proposed that the addition of the drug to ACEIs reduces protein/creatinine ratio of 57%, compared to 24% in group taking placebo (18). Numerous authors believe that aldosterone worsens the renal damage through an accumulation of growth factors and progression of degeneration of extracellular matrix, while spironolactone prevents from gene expression responsible for the regulation of extracellular matrix in the kidney. In this way, it may cease the progression of albuminuria and glomerulosclerosis. On the other hand, the RAS system cannot be completely inhibited by ACEIs and ARBs due to aldosterone escape phenomena (15, 16). The use of spironolactone can prevail over this phenomenon. The current clinical trial also corroborated that aldosterone inhibition could reduce renal damage in diabetes, even though the drug was used for a short 1 month duration. There are a few studies which have assessed other aldosterone inhibitors such as eplerenone for this purpose. Their results have been promising, too (4).

In the present study, the recommended drug regimen does not adversely influence blood pressure. Moreover, no patients developed symptomatic or severe (systolic blood pressure less than 90 mmHg) hypotension during the study. This is in contrast with the study of Davidson and Schjoedt who have found significant drop in systolic blood pressure during their studies (2, 4).

However, Rossing et al. and Van den Meiracker have reported the same results (19, 20). The suggested drug combination has not also considerable adverse effect on diastolic blood pressure. This agrees with the studies of saklayen and Rossing (18, 19). Van den Meiracker has found a minor drop in diastolic blood pressure in his patients too (20). Hyperkalemia is a remarkable adverse effect of spironolactone, particularly in renal failure, or if it is used with ACEIs. The changes in serum potassium concentrations were not statistically significant in our patients. All the patients had serum potassium concentration lower than 4.5 mmol/dl. Our finding goes up against the studies of Saklayen et al. Bianchi et al. and Van den Meiracker et al. that have reported significant rise in serum potassium concentration after treatment with spironolactone (18, 20, 21). Furthermore, one from the 21 patients in the study of Rossing et al, and 5 from the 29 patients in the case group in addition to 1 from the 30 patients in the placebo group in study of Van den Meiracker et al. were excluded from the study because of hyperkalemia (19, 20). The study of Bianchi et al. also demonstrated 0.8 mmol/dl rise in serum potassium concentration after one year treatment with spironolactone (21).

Glomerular filtration rate (GFR) dropped a little in both groups in the present study, though there was no significant difference between the groups. It opposes to the studies of Saklayen et al. and Van den Meiracker et al. who have reported significant fall in GFR in the control group, whereas, it is comparable to the study of Davidson et al. (2, 18, 20). Bianchi et al. have reported that GFR decreased more prominently in the case group compared to control group after 1 month treatment, but the reverse occurred after 1 year treatment (21).

The results of the present study verify that low to moderate doses of spironolactone augments the effect of ACEIs in the prevention of diabetic nephropathy, a grave and quite common complication of DM, without any considerable side effects. It is recommended that the use of spironolactone is taken into account when the physicians visit patients with the risk of diabetic nephropathy. Further studies with higher doses of spironolactone or in combination with other ACEIs can clarify more its efficacy in diabetic nephropathy.

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Conflict of Interest: The authors designate that there is no conflict of interest.

References

1. International Diabetes Federation. Diabetes Prevalence - Country Rankings. Availible at: http://www.allcountries. org/ranks/ diabetes-prevalence-country-ranks. Html. accessed Jan 20, 2010.
2. Davidson MB, Wong A, Hamrahian AH, Stevens M, Siraj ES. Effect of spironolactone therapy on albuminuria in patients with type 2 diabetes treated with angiotensin-converting enzyme inhibitors. Endocr Pract. 2008; 14: 985-92.
3. Shahbazian H, Shahbazian H, Feghhi M, Ehsanpour A. A study on the effect of dual blocked of rennin and angiotensin systems in contoral of diabetic nephrophaty in patients with type 2 diabetic patients. Jundishapour Sci Med J 2009; 7: 90. [In Persian]
4. Schjoedt KJ, Rossing K, Juhl TR, et al. Beneficial impact of spironolactone in diabetic nephropathy. Kidney Int 2005; 68: 2829-36.
5. Carey RM, Siragy HM. The intrarenal renin-angiotensin system and diabetic nephropathy. Trends Endocrinol Metab 2003; 14: 274-81.
6. Navarro-González JF, Mora-Fernández C, Muros de Fuentes M, García-Pérez J. Inflammatory molecules and pathways in the pathogenesis of diabetic nephropathy. Nat Rev Nephrol. 2011; 7: 327-40.
7. ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. Ann Intern Med 2001; 134: 370-9.
8. Chan JC, Ko GT, Leung DH, et al. Long-term effects of angiotensin-converting enzyme inhibition and metabolic control in hypertensive type 2 diabetic patients. Kidney Int 2000; 57: 590-600.
9. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000; 355: 253-9.
10. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; 345: 861-9.
11. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001; 345: 851-60.
12. Parving HH, Lehnert H, Brøchner-Mortensen J, et al. Effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. Ugeskr Laeger 2001; 163: 5519-24. [In Danish]
13. Andersen S, Tarnow L, Rossing P, Hansen BV, Parving HH. Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. Kidney Int 2000; 57: 601-6.
14. Lewis EJ. The role of angiotensin II receptor blockers in preventing the progression of renal disease in patients with type 2diabetes. Am J Hypertens 2002; 15, 123S-128S.
15. Mohamed RH, Abdel-Aziz HR, Abd El Motteleb DM, Abd El-Aziz TA. Effect of RAS inhibition on TGF-beta, renal function and structure in experimentally induced diabetic hypertensive nephropathy rats. Biomed Pharmacother 2009 Oct 24.
16. Sato A, Hayashi K, Naruse M, Saruta T. Effectiveness of aldosterone blockade in patients with diabetic nephropathy. Hypertension 2003; 41: 64-8.
17. Kidney Disease outcomes Qudity intiative (K/DOQI). K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic kidney Disease. Am J Kidney Dis 2004; 43: S1-290.
18. Saklayen MG, Gyebi LK, Tasosa J, Yap J. Effects of additive therapy with spironolactone on proteinuria in diabetic patients already on ACE inhibitor or ARB therapy: results of a randomized, placebo-controlled, double-blind, crossover trial. J Investig Med 2008; 56: 714-9.
19. Rossing K, Schjoedt KJ, Smidt UM, Boomsma F, Parving HH. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: a randomized, double-masked, cross-over study. Diabetes Care 2005; 28: 2106-12.
20. Van den Meiracker AH, Baggen RG, Pauli S, et al. Spironolactone in type 2 diabetic nephropathy: Effects on

proteinuria, blood pressure and renal function. J Hypertens 2006; 24: 2285-92.
21. Bianchi S, Bigazzi R, Campese VM. Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. Kidney Int 2006; 70: 2116-23.