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Assessment of Spironolactone Effects on the Prevention of Progression of Proteinuria in Chronic Kidney Diseases

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Abstract

Background: Chronic kidney disease is a persistent disorder in kidney function. This is a progressive disorder characterized by arterial hypertension, glomerular hypertension, proteinuria and some other signs; controlling any of them can reduce the progression of chronic kidney disease. In chronic kidney disease, proteinuria is used as a measure for monitoring nephron injuries and its response to treatment. Angiotensin converting enzyme inhibitors and Angiotensin receptor blockers can reduce the progression of chronic kidney disease by inhibition of Renin-Angiotensin-Aldosterone system and reduction of glomerular pressure and controlling proteinuria. However, none of them can control plasma aldosterone level appropriately. Aldosterone produces Transforming growth factor-b (TGF-b), which induces proliferation of fibroblasts and glomerulosclerosis and accelerates chronic kidney disease. Aldosterone antagonist can increase useful effects of angiotensin-converting-enzyme inhibitor (ACEI) and Angiotensin receptor blockers (ARB) Drugs.

Objectives: The study was designed to assess the effects of spironolactone as the aldosterone antagonist combined with ACEI or ARB drugs to reduce proteinuria in chronic kidney disease to prevent its progression.

Patients and Methods: This was a semi-experimental without control study. Eighty patients treated for at least two months with ACEI or ARB with uncontrolled proteinuria above 0.9g/dL were treated with 25mg/d spironolactone for two months. 24-hour urine protein and some other variables were measured at the beginning of the study, after two months treatment and one month after discontinuing the treatment.

Results: Administration of 25 mg/d spironolactone combined with ACEI or ARB for two months led to mean reduction of 24 h-urine protein from 2796.1 to 1857.4. No hyperkalemia or change in glomerular filtration rate occurred. One month after discontinuation of spironolactone, proteinuria returned to baseline level. Persistence of reduction in proteinuria in patients receiving ARBs was more than those taking ACEIs.

Conclusions: Spironolactone combined with ACEIs or ARBs leads to reduction of proteinuria in chronic kidney disease and therefore reduction of progression of the disease.

Keywords: Spironolactone, Proteinuria, Angiotensins, Aldosterone, Chronic Kidney Disease

1. Background

Chronic kidney disease (CKD) is a persistent disorder in the kidney function so that the kidney cannot maintain the normal values of protein metabolic products such as urea, blood pressure, hematocrit and acid-base equilibrium. At last, it leads to end stage renal disease (ESRD), which needs kidney replacement treatment such as dialysis or kidney transplantation (1). These patients are often symptom-free until the final stages of disease, but have numerous laboratory changes such as proteinuria (1). Risk factors of chronic kidney disease are hypertension, diabetes, aging, family history of kidney disease, history of acute kidney disease, proteinuria and structural disorder of urinary tract (2). Global prevalence of CKD is unknown and estimations are minimal. As prevalence of diabetes is high and it is highly correlated with CKD, we expect the increase of kidney disease in the future (3). According to NHANES in 1999 - 2004, about 16.8 % of the US population aged more than 20 years are affected by CKD. It was 14.5 % in 1988 - 2004 (4). About 25 - 30 million people in US and tens of millions in the world have CKD, both in developed and developing countries (5, 6). Mean age of occurrence of ESRD is 32 - 42 years in developing and 60 - 63 years in developed countries.

In glomeruli, most of the large proteins and all cells es-

cape from filtration by the physicochemical barrier, which depends on the size of the hole and its negative bacteriostatic characteristic. Electric charges and the sizes of molecules practically inhibit the passage of albumin, globulin and other heavy molecules from glomerular wall. If this barrier is damaged, plasma proteins are filtered to urine which is called proteinuria (7). Smaller proteins are reabsorbed after filtration to tubules. As a result, in a normal person, less than 150 mg protein is excreted via urine during 24 hours. Protein excretion is due to CKD and accelerates the progression of CKD (8, 9).

Practically, numerous factors play a role in the progression of chronic kidney disease including reduction of glomerular filtration rate (GFR), proteinuria, hypertension, anemia, low birth weight or prematurity, hyperuricemia, hyperlipidemia and metabolic acidosis (10). Therefore, one of the recommended management protocols for chronic kidney disease is reduction of proteinuria (11). Up to now, RAAS blockers such as ACEIs and ARBs have had the most significant effect on the reduction of progression of proteinuria and risk of ESRD. They are the standard managements in proteinuric CKD patients. They reduce proteinuria by reducing the intraglomerular pressure (12-14). Both ACEIs and ARBs reduce proteinuria significantly by 20% to 30% (15). The roles of these factors in reducing albuminuria and proteinuria and reduction of progression of CKD have been assessed by controlled clinical trials (16-20). Hyperkalemia is the side effect of both drugs and is more prominent in the combination of the two (21). Moreover, in the recent years, there has been special attention given to the effects of spironolactone in the reduction of proteinuria. For example, in numerous studies, it has been shown that the effects of ACEIs in the reduction of proteinuria in CKD patients are significantly increased when combined with spironolactone (16-21). The effects of spironolactone combined with ARBs and/or ACEIs in reducing proteinuria and the delay in the progression of CKD have been studied as well. These studies have shown that the combination is very useful and reduces proteinuria significantly (22-24), but there were doubts because of hyperkalemia as the side effect since it was increased in the studies. Four weeks after discontinuation of spironolactone, proteinuria returned to its initial level. The level of proteinuria was directly related to the level of aldosterone (23, 24).

2. Objectives

We studied the effect of spironolactone on proteinuria in CKD patients taking ARBs or ACEIs in a two-month period. We also studied the effect of this drug on GFR, Blood Urea Nitrogen (BUN), creatinine and potassium.

3. Patients and Methods

The study was a quasi-experimental without control study performed on 80 patients at Golestan hospital and three clinics of Ahvaz in Iran. The patients signed a written consent to participate in the study. The proposal of the study was confirmed by the ethical committee of research deputy of the university (number 9109/20/8 p of the committee) using the Ethical guidelines of the 1975 Declaration of Helsinki. Spironolactone as 25 mg tablet (manufactured by Aburaihan Drug Company, Iran) was administered once daily. Inclusion criteria were chronic kidney disease with GFR > 20 and proteinuria > 0.9 g/24 h. Exclusion criteria were history of hypersensitivity to spironolactone, potassium > 5.5 meq/L and history of hepatic cirrhosis. A half of patients received ACEIs and the others ARBs for at least two months without controlling proteinuria. Spironolactone, 25 mg/d, was administered to all patients for two months. Three patients were excluded from the study because of the side effects of spironolactone. 24 h-urine protein, potassium, creatinine, BUN and GFR were measured three times during the study at baseline, after two months treatment with spironolactone and one month after discontinuation of spironolactone, all at the same laboratory using the same kit. After discontinuation of spironolactone, patients continued their previous drugs (ACEIs or ARBs). Main statistical tests used were paired t-test and independent t-test. Significance level was 0.05. All analyses were performed using SPSS v.16.

4. Results

Paired t-test was used for comparing the baseline measures with the measures of two months after treatment, and also for comparing the measures of two months after treatment with the results of one month after discontinuation of spironolactone. Non-significant results reported as NS. Forty seven (58%) of patients were male and 33 (41.2%) female. Mean age of patients was 54.5 years, with 31 as the minimum and 75 as the maximum. Three patients were excluded from the study. Patients taking ARB and those taking ACEI had no significant difference in male and female ratios (P Value = 0.173). The mean age was the same for the two groups (P Value = 0.11). The mean of studied variables are shown in Table 1.

Spironolactone reduced proteinuria after eight weeks of treatment. As seen in Table 2, reduction is nearly the same in both groups taking ACEI or ARB (P Value = 0.393). One month after discontinuation of spironolactone, proteinuria increased again with a significant difference with the treatment period with spironolactone. Of course, the reduction effect of ARB was more persistent than ACEI, as

Table 1. "Baseline", "After Two Months", and "One Month After Discontinuation" Data for Study Variables[a,b]

Variable	Baseline	After two months	P Value [c]	After two months	One month after discontinuation	P Value [d]
24h-urine protein	2808 ± 1169.8	1857.4 ± 696.5	0.000	1874.9 ± 694.2	2684 ± 1296.9	0.000
GFR	71.3 ± 15.5	69.1 ± 14.53	NS3	68.68 ± 14.46	69.93 ± 14.35	NS
potassium	4.54 ± 0.58	4.61 ± 0.59	NS	4.62 ± 0.52	4.61 ± 0.47	NS
BUN	23.93 ± 8.06	23.79 ± 7.74	NS	23.86 ± 7.77	23.92 ± 7.31	NS
Creatinine	1.5 ± 0.38	1.57 ± 0.29	0.02	1.57 ± 0.26	1.46 ± 0.29	0.03

[a] Data are presented as SD ± mean.
[b] Abbreviations: NS, non-significant.
[c] Comparison of "baseline" and "after two months" measures (3 patients excluded; 77 studied).
[d] Comparison of "after two months" and "one month after discontinuation" measures (two other patients excluded; 75 patients studied).

seen in Table 3 (P Value = 0.007). GFR, BUN and potassium had no significant change. Creatinine had a statistical significance, but not clinical.

Table 2. Comparing Mean of Differences in Proteinuria in Patients Taking ARB or ACEI After Two Months Treatment With Spironolactone[a]

Drug Used	Count	Values [b]
ARB	38	998.1 ± 657.22
ACEI	39	880.7 ± 537.03

[a] P = 0.393.
[b] Data are presented as mean ± SD.

Table 3. Comparing Mean of Differences in Proteinuria Between "After Two Months Treatment" and "One Month After Discontinuation of Spironolactone" in Patients Taking ARB or ACEI[a]

Drug Used	Count	Values [b]
ARB	38	554.86 ± 747.64
ACEI	39	1056.58 ± 825.39

[a] P = 0.007.
[b] Data are presented as mean ± SD.

5. Discussion

Aldosterone is a mineralocorticoid hormone secreted from adrenal glomerulosa with a vital role in electrolyte homoeostasis. Aldosterone causes proteinuria by damaging kidney glomeruli by activating plasminogen activator inhibitor and producing TGFB and proliferation of fibroblasts and creating fibrosis in glomeruli. It also increases reabsorption of sodium, increases blood pressure and capillary pressure of glomeruli (25). Studies have shown that adrenalectomy in rats decreases proteinuria (26) and administering oxygen desoxycorticosterone to them causes nephrosclerosis (27). These studies made a basis for using aldosterone antagonist for prevention of the progression of CKD. Of course, their side effect, hyperkalemia, has always been noticed. Treatment with these drugs to reduce the excretion of protein slows the progression of kidney disease (28, 29). In 2005, Sato and colleagues administered 25 mg/d spironolactone for 3 months to 32 CKD patients with proteinuria 0.5 g/d and GFR > 85 treated with ARB for 6 months. After 3 months, proteinuria was reduced but no significant change in hyperkalemia, blood pressure or GFR was detected. The number of patients in this study was low and the GFR level was very high; in fact patients in the initial stages of CKD with lower risk were studied (30).

In 2001, Chrysostomou and Colleagues in a study without control group administered 25 mg/d spironolactone with ACEIs to 8 diabetic nephropathy patients with persistent proteinuria for 6 weeks. After 4 weeks, proteinuria was decreased by 54% without any significant changes in potassium level. The strength of the study was that its duration was six months but the weak point of the study was that the number of patients was low and there were only diabetic patients in the study (31).

In a prospective randomized study in 2006, Bianchi and his colleagues administered ACEIs and spironolactone to 83 CKD patients for one year receiving ACEIs for proteinuria but it was not controlled. Control group included 82 patients with CKD who only used ACEIs for one year. No significant change in proteinuria was seen in the control group but in the main study 83 patients, proteinuria decreased from 2.1 to 0.8 gram per day (16). The duration of the study was long. Hyperkalemia was not observed, which might be due to low dose of spironolactone.

In 2006, Chrysostomou and Colleagues in a double-blind clinical trial studied 41 patients with proteinuria more than 1.2 g/d and showed that spironolactone in combination with ACEi is a valuable treatment (17). In some other studies, number of patients was enough, but GFR

was high indicating the initial stages of CKD (18). In 2005, Rossing and colleagues in a two-month crossover double-blind randomized study found that administering 25 mg/d spironolactone in combination with ACEIs and/or ARB in patients with GFR > 30 reduces albuminuria and blood pressure and therefore prevents the progression of kidney and cardiovascular disease in type 2 diabetic nephropathy. The mean of potassium was normal and since the spironolactone was low and the duration of study was short, it was probably due to the low GFR. GFR was not reduced (19).

In 2005, Schjoedt and colleagues in a crossover double-blind clinical trial with 25 mg/d spironolactone and placebo for two months in 20 type 1 diabetic patients with albuminuria despite taking antihypertensive treatment found that administering spironolactone reduced blood pressure and had protective effect in type 1 diabetic nephropathy (20). The number of patients was not enough. Hyperkalemia was not seen indicating safety of spironolactone. In 2002, Epstein showed that aldosterone inhibitor has protective effect for the kidney (23). In 2005, Bianchi in a short-term and low-dose study administered 25mg/d spironolactone for two months to 42 CKD patients with different causes who had GFR = 20 - 90 and proteinuria > 0.9 g/d and taking ARB and/or ACEIs for one year. After two weeks, proteinuria was reduced and the reduction continued until the end of the second month (22). Transient reduction was observed in GFR, which returned to baseline after discontinuation of the drug. Hyperkalemia was seen in 11% of patients, mainly in patients with GFR < 60. In the group that received both ACEi and ARB, Aldosterone level was lower than the group receiving aldosterone with ACEi or ARB. Four weeks after discontinuation of spironolactone, proteinuria level increased as high as the baseline level. The number of patients in the study was low, but the study was strong to show that spironolactone can reduce proteinuria in a short-duration (23). In 2009, Navaneethan and colleagues in a systematic review about the prevention of progression of kidney disease with aldosterone antagonists using Medline data base concluded that in patients who received ACEi or ARB, aldosterone antagonists reduced proteinuria, although the risk of hyperkalemia increased (24). In 2008, Bomback and colleagues in a systematic review showed that most studies about spironolactone have these characteristics in common: CKD with different causes, Low number of patients studied (less than 30), mean of GFR > 60 and potassium cutoff equal to 5.5. In most studies, blood pressure did not decrease. No significant hyperkalemia was seen (32).

In our study, we showed the role of spironolactone in reducing proteinuria in patients taking ACEIs or ARBs and the mean reduction was the same in both groups. It is considered that it potentiates the effects of ARBs or ACE inhibitors in the prevention of progression of chronic kidney diseases. GFR reduction was not seen. Accurate monitoring of potassium in patients taking spironolactone in the study showed no hyperkalemia. Although no significant hyperkalemia was seen, monitoring and measurement of potassium is recommended in all patients taking spironolactone, especially in combination with ACEIs or ARBs. Limitations of our study were no assessment according to GFR levels, no control group, short duration of the study and no attention to aldosterone escape.

Spironolactone can reduce proteinuria and prevent the progression of CKD, often without significant changes in GFR or hyperkalemia. We showed that adding spironolactone to ACEIs or ARB can effectively reduce proteinuria.

Future studies with more participants, longer duration and clinical trial design are recommended. Assessing aldosterone escape and analysis according to GFR levels are recommended as well.

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