Angiotensin Receptor Blocker and N-Acetyl Cysteine for Reduction of Proteinuria in Patients With Type 2 Diabetes Mellitus

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Introduction. Proteinuria and albuminuria are established risk factors for progressive renal damage. Albuminuria can be effectively controlled by antihypertensive drugs that interrupt the renin-angiotensin-aldosterone system. However, the efficiency of N-acetyl cysteine (NAC) in preventing diabetic nephropathy is uncertain. Renoprotective effects of angiotensin receptor blockers and NAC in preventing or reducing of proteinuria in patients with diabetic nephropathy was studied.

Materials and Methods. In a randomized controlled trial, 70 patients with type 2 diabetic nephropathy (proteinuria and renal insufficiency) were studied. The patients were randomly divided into two groups and were treated with losartan, 25 mg, twice per day, with and without NAC, 600 mg twice daily (study and control groups, respectively; 35 patients in each group). Urine protein was checked before treatment and after 2 months of treatment.

Results. The two groups were comparable regarding gender, age, serum creatinine, and urine protein excretion levels. Proteinuria improved in both groups. The mean proteinuria level decreased more in patients with losartan and NAC; however, comparison of proteinuria between the two groups showed no significant difference after 2 months.

Conclusions. Angiotensin receptor blockers reduced proteinuria due to diabetic nephropathy, and this study failed to detect additional effect when NAC was combined with these medications.

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INTRODUCTION

Diabetic nephropathy is one of the most important causes of chronic renal damage. It has a strong relationship with cardiovascular diseases. Proteinuria increases mortality and morbidity rate in these patients.[1] In 1980, it was suggested for the first time that excretion of albumin, even in small amounts (assessed by sensitive protein-measuring methods), may be regarded as an important predicting factor in renal insufficiency of patients with types 1 and type 2 diabetes mellitus (DM). Microalbuminuria is the major feature of the earlier stages of renal involvement.[2] Proteinuria is seen in about 15% to 40% of type 1 diabetic patients. The prevalence is more variable in type 2 DM and occurs in about 5% to 20% of patients. However, the number of patients with type 2 DM is increasing, maybe due to better managing of these patients.

According to previous studies, blockage of renin-angiotensin-aldosterone system (RAAS) leads to

stabilization or prevention of diabetic nephropathy. However, follow-up of the patients with type 2 DM has demonstrated that moving toward chronic renal damage is often seen due to increasing number of these patients, and this important complication of DM wastes a great amount of health expenditures in all parts of the world.[3-5] Angiotensin-receptor blockers (ARBs) reduce renal capillary pressure with blocking of RAAS and prevent microalbuminuria progression, and ultimately, chronic renal damage.[6] Many different studies have revealed that ARBs prevent or reduce proteinuria and chronic renal damage in type 2 diabetic patients.[7-9] Parving and colleagues showed that ARBs prevent progression of microalbuminuria towards macroalbuminuria.[10]

Oxidative stress is a well known phenomenon in exacerbation of diabetic nephropathy. It is shown that some antioxidant agents like vitamin E, vitamin C, and statins reduce proteinuria in diabetic patients. Human studies using antioxidative agents like N-acetyl cysteine (NAC) are not frequent. The majority of studies published to date are on animal models. Most of the human studies are on NAC effects in reducing of chronic kidney disease progression speed. N-acetyl cysteine is an antioxidant and relative vasodilator. This drug revealed reduction of ischemia in acute kidney damages, improved glomerular filtration rate (GFR), and shortened recovery period in different experimental animal studies.[11-14] Renal toxicity of contrast agents remains an up-to-date challenge.

Studies of human being on the role of NAC in the treatment of diabetic nephropathy and proteinuria is not frequent and findings are controversial.[15-18] Effective role of RAAS-blocking drugs in diabetic patients with proteinuria and diabetic nephropathy is established. To further investigate optimal therapies for proteinuria in DM, we studied a combination of ARBs and NAC in comparison with ARBs alone.

MATERIALS AND METHODS

This randomized controlled trial was conducted in Imam Reza Hospital, Sina Hospitals, and Sheikholraeis Subspecialized Clinic, affiliated to Tabriz University of Medical Sciences, Tabriz, Iran, from September 2010 to May 2011. Seventy patients with type 2 DM were enrolled in this study. All of them had been referred to our centers at different stages of diabetic nephropathy. These patients were randomly divided into 2 groups (each consisted of 35 patients). All of the participants had documented proteinuria; their 24-hour urine protein level was higher than 300 mg. The exclusion criteria were nonadherence to medications, a serum creatinine level greater than1.8 mg/dL, and underlying disorders other than diabetic nephropathy that would affect kidney function and proteinuria (such as glomerulonephritis, pyelonephritis, interstitial nephritis, and other glomerulopathies). Eligible patients who provided informed consent were included in the study.

Urinalysis and measurement of FBG, hemoglobin A1c, and 24-hour urine protein levels were carried out before intervention. After a 1-month washout period for ARBs and angiotensin-converting enzyme inhibitors, both groups were started on losartan, 25 mg, twice daily, and the study group also received NAC, 600 mg, twice daily, for a time period of 2 months. All laboratory studies were repeated after the two-month study period.

The data were analyzed using descriptive statistical methods and continuous values were reported as mean ± standard deviation. The chi-square test was used to study qualitative variables. The Mann-Whitney U test was used for comparison of nonparameteric quantitative variables. For comparisons between values before and after the treatment period, the Wilcoxon signed rank test was utilized. The SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, Ill, USA) was used for data analyses and a P value less than .05 was considered significant.

RESULTS

A total of 70 patients with type 2 DM (mean age, 61.8 ± 8.5 years; range, 40 to 78 years) were enrolled. Thirty-three patients were men (47.1%). Patients in the study group (losartan in combination with NAC) had a mean age of 60.2 ± 10.1 years, and those in the control group (losartan only) were 63.4 ± 6.4 years old (P = .10). Baseline characteristics of the participants are presented in the Table. The baseline mean FBG level was 174.9 ± 41.1 mg/dL in the study group and 193.4 ± 54.1 mg/dL in the control group (P = .10). Serum levels of hemoglobin A1c were 8.6 ± 1.6% and 9.2 ± 1.6% in the study and control groups, respectively (P = .09).

Proteinuria and serum creatinine levels were comparable between the two groups at baseline

Baseline Characteristics and Laboratory Data of Participants

Variable	Study Group (n = 35)	Control Group (n = 35)	*P*
Age, y	60.2 ± 10.1	63.4 ± 6.4	.10
Gender			
Male	19	20	
Female	16	15	.08
Fasting blood glucose, mg/dL	174.9 ± 41.1	193.4 ± 54.1	.10
Hemoglobin A1c, %	8.6 ± 1.6	9.2 ± 1.6	.09
Proteinuria, mg/24 h	1435.0 ± 247.3	1027.6 ± 367.9	.70
Serum creatinine, mg/dL	1.53 ± 0.51	1.61 ± 0.49	.10

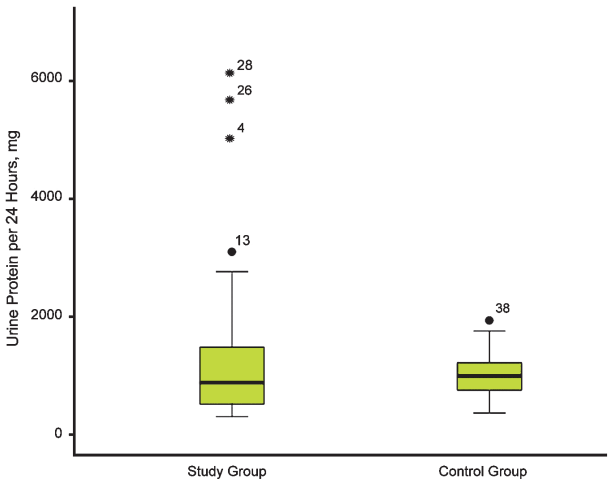

Figure 1. Comparison of proteinuria before therapy between the study and control groups.

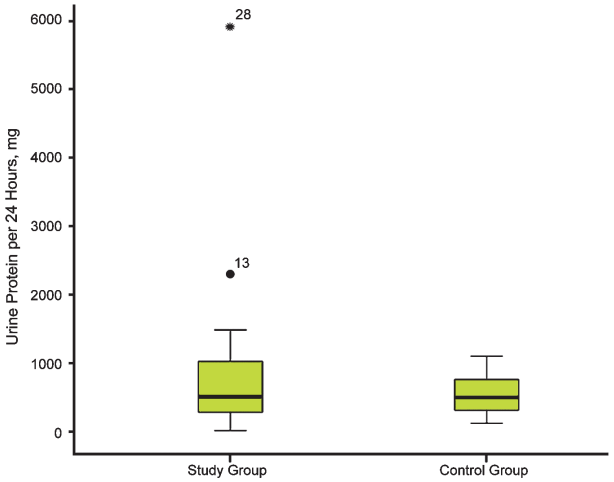

Figure 2. Comparison of proteinuria after therapy between the study and control groups.

(24-hour urine protein level, 1435.02 ± 247.30 mg versus 1027.6 ± 367.9 mg, respectively; *P* = .70). The effect of losartan alone in reducing proteinuria is depicted in Figure 1; proteinuria was significantly reduced within 2 months of treatment. Losartan reduced proteinuria to 417.2 ± 121.1 mg/24 h in the control group (*P* = .005). In the study group, a combination of losartan and NAC administration decreased proteinuria to 521.1 ± 169.3 mg/24 h (*P* = .05). There was no difference in urine protein excretion level after the treatment between the two groups (*P* = .50; Figure 2).

DISCUSSION

It is estimated that more than 150 million people suffer from type 2 DM and its complications, and that its prevalence will be doubled during the next 25 years.[19,20] Many different researchers like de Zeeuw and colleagues have shown that treatment of type 2 DM with losartan is really efficient and leads to considerable decreasing of albuminuria. Diminishing of albuminuria in a 6-month therapeutic period can be regarded as the effective control of the RAAS.[21,22] This system—an independent risk factor predicting renal damages—is well suppressed by ARBs.[21,22] Viberti and coworkers used 80 mg of valsartan per day and showed that albuminuria was decreased significantly.[23] Also, Eijkelkamp and colleagues demonstrated that ARBs decreased albuminuria in 51% of diabetic patients within a 6-month follow-up period.[24] In a randomized controlled trial, Rossing and associates proved usefulness of ARBs in decreasing of albuminuria and proteinuria of patients with type 2 DM.[25]

On the other hand, in many meta-analysis studies contrast nephropathy was shown to be prevented by NAC.[26,27] According to our study, administration of ARBs and ARBs along with NAC for 8 weeks were effective in decreasing 24-hour urine protein level. However, comparing these two forms of therapies did not show any significant difference. Thus, blocking of angiotensin receptor alone was as effective as the use of ARBs and NAC.

Angiotensin II and oxidative stress lead to progression of glumerolonephritis by producing nicotinamide adenine dinucleotide phosphate oxidase.[28,29] N-acetyl cysteine has considerable effects on free radicals and oxidative stress. Also it has additional vasodilation effects. Plasminogen inhibitors have an important role in extracellular

matrix fixing. Hyperglycemia promotes plasminogen inhibitors and induces free oxygen radicals. These phenomena hurt the glomerular mesangial cells in diabetic patients. Lee and colleagues studied protective effects of NAC in this condition.[30] They showed that NAC effectively reduced plasmingen inhibitors levels and diminished free oxygen radicals. They concluded that NAC was effective in molecular level but further clinical studies was recommended.[30] Lee and colleagues showed that NAC led to oxidative stress system suppression and production of intermediate metabolites of free radical, which significantly decreased these agents in patients with greater blood glucose levels.[30] Trends towards using of NAC due to its antioxidative effects has been increasing.[31] In animal models of Pieper, antioxidants and NAC in mice, 48 hours of administration of streptozotocin successfully decreased proteinuria and function of endothelial cells were preserved.[8,32] Clinically, only one study has been done for demonstration of NAC effects on proteinuria of diabetic patients, which revealed no effect of this drug on proteinuria of diabetic patients.[7] According to the results of this study, there was no significant difference in proteinuria before and after and even during follow-up period of NAC administration. However, some animal models and in vitro studies demonstrated useful effects of NAC in decreasing oxidative stress and regulating of kidney mesangial cells recovery. In our study, effects of 8-week treatment with NAC along with ARBs was evaluated on proteinuria of patients with type 2 DM; no significant difference was observed as compared ARBs alone. Decreasing of proteinuria was almost the same for both groups and adding of NAC had no extra advantages.

Diabetes mellitus is a chronic disease and because of long-time exposure of glomeruli to higher levels of glucose, we suggest studies with longer time periods and greater sample sizes for better clarifying of NAC effects on diabetic patients. We did not measure the oxidative stress levels after NAC administration and we suggest measuring of these agents in future studies.

CONCLUSIONS

In line with previous reports, results of the present study revealed that the use of ARB in diabetic patients with proteinuria is effective and useful in reducing protein excretion, and it failed to show any additional effect when an ARB was combined with NAC among diabetic patients with proteinuria.

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