საქართველოს მეცნიერებათა ეროვნული აკადემიის მოამბე, ტ. 5, №1, 2011
BULLETIN OF THE GEORGIAN NATIONAL ACADEMY OF SCIENCES, vol. 5, no. 1, 2011

Medical Sciences

Novel Approaches to Prevention of Chronic Kidney Disease in Patients with Metabolic Syndrome

Nodar Kipshidze*, Tea Gamezardashvili**

**Academy Member, Academician Nodar Kipshidze National Center of Therapy, Tbilisi*
*** Academician Nodar Kipshidze National Center of Therapy, Tbilisi*

ABSTRACT. Metabolic syndrome (MS) is a major public health threat. Individuals with MS are at increased risk for development of chronic kidney disease (CKD). Despite effective medical interventions that have targeted vascular renin-angiotensin system (RAS) blockade the prevalence of CKD remains considerably high. Few studies have directly compared the reno- protective effects of Angiotensin II-receptor blockers and Angiotensin-converting-enzyme inhibitors (ACE) in patients with MS. The aim of the present study was to compare the renoprotective effects of Angiotensin II-receptor blockers and Angiotensin-converting-enzyme inhibitors (ACE) in patients with MS and early nephropathy. In this prospective three year study, we randomly assigned 123 patients (mean age 45.8±11.7 years, range 31-57 years, 72 male and 51 female) with metabolic syndrome and early nephropathy to receive either the ACE inhibitor Quinapril (Accupro, Pfizer International, 20mg daily, 43 subjects) or Angiotensin II- receptor blocker Valsartan (Diovan, Novartis, 160 mg daily, in 41 subjects) or in combination Valsartan / Quinapril (160 mg/20 mg daily, in 39 subjects). The endpoint was the change in the glomerular filtration rate (GFR) (determined by measuring the plasma Clearance of Creatinine) between the baseline value and the last available value during the three-year treatment. After three years, indices of GFR increased by 4.2 ml/min/1.73m² in Quinapril-treated patients, compared with - 4.7 ml/min/1.73m² in Valsartan-treated subjects, and - 7.1 ml /min/ 1.73m² in Valsartan /Quinapril group ($p<0.01$). The results indicated that Valsartan was not superior to Quinapril, but the renoprotective effects of the combined therapy with Valsartan/Quinapril significantly improved after three years. *© 2011 Bull. Georg. Natl. Acad. Sci.*

Key words: *metabolic syndrome, chronic kidney disease, Angiotensin II-receptor blocker, Angiotensin-converting-enzyme inhibitor.*

Metabolic syndrome (MS) is a major public health threat for 20 percent of the population 30 years of age and older [1]. Excess body fat, especially abdominal visceral fat accumulation, is frequently accompanied by diabetes mellitus, dyslipidemia, and hypertension, and could result in atherosclerotic vascular diseases.

Individuals with MS are at increased risk for development of chronic kidney disease (CKD) [2]. The prevalence of CKD may increase for several reasons. The prevalence of two greatest causes of CKD, diabetes mellitus and hypertension, is increasing and are aggravated by obesity, dyslipidemia, smoking and other risk factors. Prevalence of obesity increases parallelly with chronic kidney disease (CKD). An estimated 20 million adults in the United States have CKD - about one in nine adults [3]. Several recent epidemiologic studies have shown that obesity and the metabolic syndrome are independent predictors of CKD. In addition to diabetes and hypertension, several other mechanisms have been postulated to initiate and maintain kidney injury in patients with obesity and the metabolic syndrome. Estimation of glomerular filtration rate (GFR) is the best overall index of kidney func-

tion. The level of GFR should be estimated from prediction equations that take into account the Serum Creatinine (SCr) concentration and some or all of the following variables: age, gender, race and body size. The following equations provide useful estimation of GFR according to the Cockcroft-Gault equations [4].

Our knowledge of the path physiology and treatment of MS has rapidly increased in the last decades [5-7]. Hypertension, which is closely linked to obesity [8], is probably a major cause of renal dysfunction in obese patients but is likely not to be the only hemodynamic reason. Increased vascular tone and renal salt and water retention are the main initiators of hypertension in obesity. In addition, increased RAS activity, as a result of both sympathetic activation and possibly increased adipose tissue synthesis, results in increased renal sodium and water retention [9, 10]. Despite effective medical interventions that have targeted vascular renin-angiotensin system (RAS) blockade prevalence of CKD remains considerably high. Few studies have directly compared the reno-protective effects of Angiotensin II-receptor blockers and angiotensin-converting-enzyme inhibitors (ACE) in patients with MS.

The aim of the present study was to assess whether angiotensin-converting-enzyme inhibitors, Angiotensin II- receptor blockers or their combination prevent CKD in subjects with MS.

Material and Methods

This study was conducted in Acad. Nodar Kipshidze National Center of Therapy. The study investigates indices of GFR in patients with MS and early nephropathy who were randomly assigned to receive Quinapril and/or Valsartan during the Follow-Up study. In total 123 patients were studied (mean age 45.8±11.7, range 31-57 years, male -72 and female-51). Every patient was kept on a diet and treated with Metformine. All patients had mild-to moderate hypertension and serum creatinine level was below 1.6 mg/dl (Table 1).

Table 1.

Baseline Characteristics of the subjects

Variable	Quinapril group (N=43)	Valsartan group (N=41)	Valsartan/ Quinapril group (N=39)
Age - year	42.8±11.7	45.2±10.9	44.9±10.8
Sex (male/female)	24/19	23/18	25/14
Body-mass index	31.6±3.8	31.9±4.1	31.2±3.5
Blood pressure - mmHG			
Systolic	158.7±14.9	154.9±15.2	158.3±15.1
Dyastolic	85.3±8.4	85.9±7.6	86.1±7.9
Cholesterol – mg/dl	-	-	-
Total – mg/dl, mean	218±41	222±38	215±40
High-density lipoprotein– mg/dl, mean	39±11	39±13	40±12
Low-density lipoprotein– mg/dl, mean	137±32	139±29	136±31
Triglycerides– mg/dl, mean	198±85	204±104	201±98
Glycosylated hemoglobin – (%), mean	7.1±0.8	7.3±0.9	6.9±1.1
Serum creatinine – mg/dl	1.11±0.27	1. 13±0.21	1.09±0.32
Glomerular filtration rate – ml/min/1.73m²	90.5±21.2	91.6±22.1	92.1±19.8
Proteinuria – no. of subj.(%)	15 (34.9)	13 (31.7)	14 (35.9)
History of cardio-vascular disease – no.(%)	21 (48.8)	19 (46.3)	20 (51.3)
hypertension history – year, median (range)	7.0 (0-18)	5.5 (0-17)	6.0 (0-16)

Table 2.

Concomitants Cardiovascular Medications Used during the Study

Medication	Quinapril group (N=43)	Valsartan group (N=41)	Valsartan / Quinapril group (N=39)
Diuretics	21 (49%)	18 (44%)	8 (20%)
Beta-blockers	19 (44%)	17 (41%)	12 (31%)
Calcium-channel blockers	22 (51%)	15 (37%)	11 (28%)
Statins	28 (65%)	29 (71%)	25 (64%)
Aspirin	26 (60%)	25 (61%)	20 (51%)
Metrformine	26 (63%)	26 (63%)	24 (62%)

During the two-week screening period patients stopped to receive antihypertensive medication and the subjects were randomly assigned to receive either Quinapril (Accupro, Pfizer International, 20 mg daily, in 43 subjects) or Valsartan (Diovan, Novartis, 160 mg daily, in 41 subjects) or in combination Valsartan / Quinapril (160 mg/20 mg daily, in 39 subjects). Additional antihypertensive medication (not an ACE inhibitor or an Angiotensin II-receptor blocker) was allowed after one month, if the resting blood pressure exceeded 160/100mmHg.

The primary end point was the change of the glomerular filtration (determined by glomerular filtration rate and serum creatinine level).

Statistical analysis - Data are presented as mean + SEM. Differences between groups were evaluated by unpaired Student's t-test. A probability value of less than 0.05 denoted the presence of statistically significant difference. All calculations were performed using SPSS for Windows, version 11.0.

Results and Discussion

The baseline characteristics of the 123 subjects who underwent randomization were similar in the three treatment groups (Table 1). 37 of the 43 subjects completed the study in the Quinapril group (86%), and 34 of the 41 (83%) subjects - in the Valsartan group, and 31 of the 39 subjects- in the Valsartan / Quinapril group (79%).

The use of concomitant cardiovascular medications increased during the study targeting the clinical guidelines (Table 2).

The GFR was measured at baseline and then yearly during three years or until dropout. After baseline, GFR was determined in 102 patients. After three years, the mean difference in the GFR was - 4.2 ml/min/1.73m² in

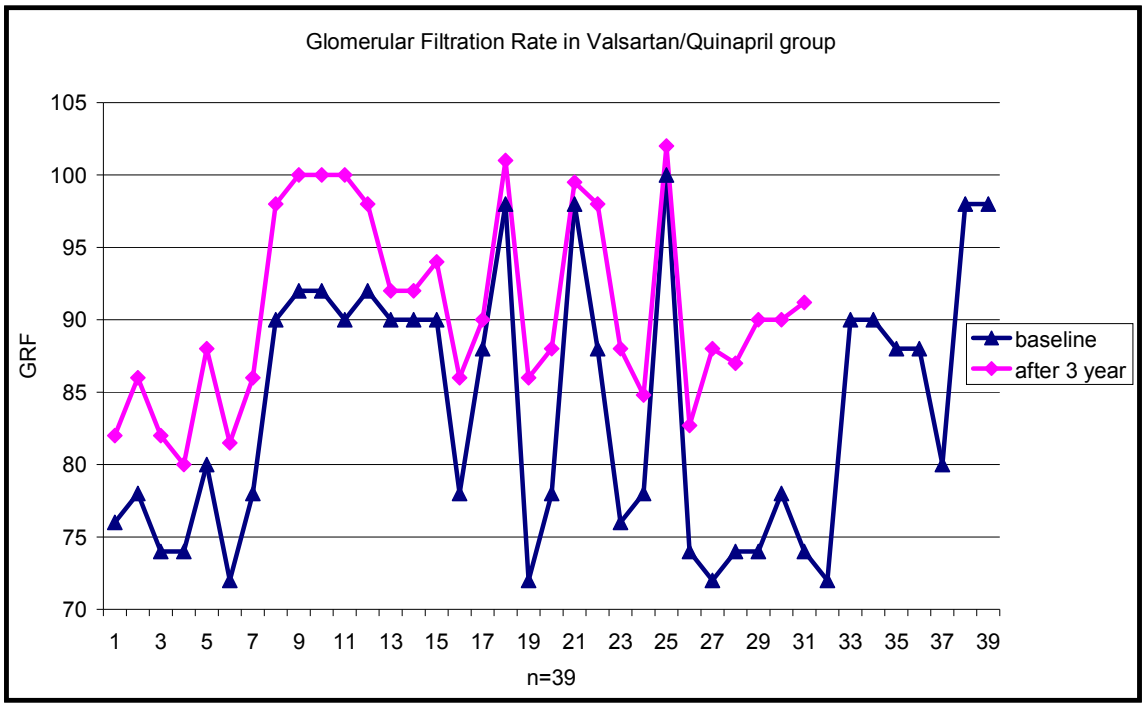

Fig. 1. Glomerular filtration rate in Valsartan/Quinapril group (n=39).

Quinapril-treated patients, compared with - 4.7 ml/min/ 1.73m² in Valsartan-treated subjects, and - 7.1 ml /min/ 1.73m² in Valsartan /Quinapril group .

Analysis of GFR difference showed a mean change of - 4.2 ml/min/1.73m² , compared with - 4.7 /min/1.73m²; significant difference was not observed between the Valsartan and Quinapril groups. Combined therapy with Valsartan /Quinapril showed a mean change of - 7.1 ml/ min/1.73m² v.s. - 4.7 ml/min/1.73m², and - 7.1 ml/min/1.73m² v.s. - 4.2 ml/min/1.73m² ($p<0.001$), which indicates that this approach is effective during the prevention and treatment of CKD (Fig.1).

In this long-term comparison of renal outcomes with use of an Angiotensin II- receptor blocker and an ACE inhibitor in subjects with MS and early nephropathy, we determined that Valsartan was not inferior to Quinapril in preventing the progression of renal dysfunction. But our study indicated that combined therapy with Angiotensin II- receptor blocker/ ACE inhibitor reduced the Serum Creatinine and increased GFR.

Weight loss and aggressive treatment of diabetes and hypertension still constitute the most effective interventions for CKD prevention. Agents that enhance insulin sensitivity, such as PPAR agonists, blockade of the RAS and HMG-CoA reductase inhibitors, are promising as adjunctive therapies to prevent progression of renal disease in patients with the metabolic syndrome [11]. Blockade of the RAS is likely to be beneficial, but treatment will need to be individualized depending on the degree of renal dysfunction and the presence of other co morbidities that are associated with abdominal obesity, such as cardiopulmonary dysfunction and perhaps the pattern of fat distribution. In addition, to identify the optimal regimens to maximize renoprotection, major efforts should be made in identifying and treating all patients at risk, with the final aim to delay or even prevent the onset and progression of chronic renal disease and related complications.

Conclusions. The long-term combined therapy with Angiotensin II- receptor blocker Valsartan/ ACE inhibitor Quinapril prevents the progression of renal dysfunction in subjects with metabolic syndrome and early nephropathy.

სამედიცინო მეცნიერებანი

მეტაბოლური სინდრომის მქონე პირებში თირკმლის ქრონიკული დაავადების პრევენციის თანამედროვე ღონისძიებები

ნ. ყიფშიძე*, თ. გამეზარდაშვილი**

** აკადემიკოსი, აკად. ნ. ყიფშიძის სახელობის თერაპიის ეროვნული ცენტრი, თბილისი*
*** აკად. ნ. ყიფშიძის სახელობის თერაპიის ეროვნული ცენტრი, თბილისი*

მეტაბოლური სინდრომი (მს) ფართოდ გავრცელებული პათოლოგიაა, რომელიც აღენიშნება 30 წელზე უფროსი ასაკის დედამიწის მოსახლეობის 20%-ს. მს აერთიანებს რა მთელ რიგ რისკ-ფაქტორებს (აბდომინური სიმსუქნე, არტერიული ჰიპერტენზია, გლუკოზისა და ლიპიდური ცვლის დარღვევა), ხელს უწყობს თირკმლის ქრონიკული უკმარისობის (თქუ) განვითარებას ახალგაზრდა ასაკში. დღეისათვის ცნობილია კვლევათა ძალზე მცირე რაოდენობა მს დროს ანგიოტენზინ II-რეცეპტორის ბლოკერების (არბ) და ანგიოტენზინის გარდამქმნელი ფერმენტის (აგფ) ინჰიბიტორების რენო-პროტექტორული ეფექტის შესახებ. ჩვენი კვლევის მიზანი გახლდათ, შეგვეფასებინა არბ-ს და აგფ-ინჰიბიტორების რენოპროტექტორული ეფექტურობა მს-ით დაავადებულ პირებში ნეფროპათიის საწყის ეტაპზე.

კვლევის ფარგლებში შესწავლილ იქნა მს მქონე 123 პაციენტი (საშუალო ასაკი 45.8±11.7წ., 72 მამაკაცი/51 ქალი). ისინი დაიყო 3 ჯგუფად. ყველა მათგანს ენიშნებოდა ათეროსკლეროზის საწინააღმდეგო დიეტა და სტანდარტული მედიკამენტოზური მკურნალობა. I ჯგუფს ეძლეოდა 20 მგ ქვინაპრილი (Ჩკუპრო, ფაიზერი), II ჯგუფს — 160მგ ვალსარტანი (დიოვანი, ნოვარტისი), ხოლო III ჯგუფს — 20 მგ ქვინაპრილი/ 160მგ ვალსარტანი. მათ უტარდებოდათ რუტინული გამოკვლევები, ისაზღვრებოდა გლომერული ფილტრაციის სიჩქარე (კრეატინინის კლირენსის მიხედვით) დასაწყისში და 3 წლიანი მკურნალობის შემდეგ.

კვლევის შედეგად სამივე ჯგუფში გამოვლინდა დადებითი დინამიკა; გლომერული ფილტრაციის სიჩქარე შეიცვალა I ჯგუფში - 4.2 მლ/წთ/1.73მ² -ით, II ჯგუფში — 4.7 მლ/წთ/1.73მ² -ით, ხოლო III ჯგუფში — 7.1 მლ/წთ/1.73მ² -ით. სტატისტიკურად სარწმუნო აღმოჩნდა III ჯგუფში მიღებული ცვლილება ($p<0.001$). მიღებული შედეგები მოწმობს, რომ არბ ვალსარტანი და აგფ ინჰიბიტორი ქვინაპრილი დადებით ზემოქმედებას ახდენენ თქუ-ის საწყის ეტაპზე მს მქონე პირებში, ამასთან ერთად, არ გამოვლინდა არბ ვალსარტანის სარწმუნო უპირატესობა აგფ ინჰიბიტორ ქვინაპრილთან შედარებით. კვლევის შედეგები მოწმობს ვალსარტანი/ ქვინაპრილი კომბინირებული თერაპიის უპირატესობას თქუ-ის საწყის ეტაპზე მს მქონე პირებში.

ხანგრძლივი კომბინირებული თერაპია არბ/აგფ ინჰიბიტორით (ვალსარტანი 160 მგ/ ქვინაპრილი 20 მგ) ახდენს თქუ-ის უკუგანვითარებას მს მქონე პირებში, ამდენად უპრიანია გამოყენებულ იქნას თქუ-ის პრევენციისა და მკურნალობისთვის.

REFERENCES

1. *H.M. Lakka, D.E. Laaksonen, T.A. Lakka, et al*. (2002), JAMA, 288: 2709-2716.
2. National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease.(2007), Am J Kidney, 49: S12-154.
3. *D.W. Cockcroft, M.H. Gault* (1976), Nephron, 16: 31-41.
4. *N. Kipshidze, T. Gamezardashvili, et al*. (2007), Journal of Clinical Lipidology, 1,5: 502.
5. *N. Kipshidze, T. Gamezardashvili, et al*. (2006), Experimental and Clinical Medicine, 5(30): 64-68.
6. *T. Gamezardashvili, N. Kipshidze, et al*. (2006), Allergology and Immunology, 7, 5:640-641.
7. *J.P. Montani, V. Antic, Z. Yang, A. Dulloo* (2002), Int J Obes Relat Metab Disord, 26(Suppl 20) :S28 -S38.
8. *I.M. Wahba, R.H. Mak* (2007), Clin J Am Soc Nephrol; 2: 550-562.
9. *M.E. Molitch, De Fronzo, M.J. Franz, et al*. (2004), Diabetes Care, 27(Suppl 1):S79-S83.
10. *P. Ruggenenti, A. Fassi, A.P. Ilieva, et al*. (2004), N Engl J Med, 351(19):1941-1951.
11. *S. Yusuf, P. Sleight, J. Pogue, et al*. (2000), N Engl J Med, 342(3):145-153.

Received September, 2010