Conclusions

Quantitative assessment of albumin concentration in serum, ascitic fluid and lymph is not an index revealing the prognosis in terms of evolution of ascites to patients with cirrhogenous decompensated cirrhosis. This study found that serum-ascites albumin gradient does not reveal a significant difference in the case of resistant and refractory ascites. Ascites albumin gradient decreases during the evolution of lymph and ascitic syndrome and has a tendency to decrease with the progression of advanced forms of ascitic syndrome. Implementation of the notion of serum-ascites-lymph albumin gradient and its significance as a criterion of evolution for ascitic syndrome requires further study and validation.

References

1. Fisher NC, Hanson J, Phillips A, et al. Mortality from liver disease in the West Midlands, 1993–2000: observational study. *BMJ.* 2002;325:312–313.
2. Ginès P, Fernández-Esparrach G. Prognosis of cirrhosis with ascites. In: Arroyo V, Ginès P, Rodés J, Schrier RW, eds. Ascites and renal dysfunction in liver disease: pathogenesis, diagnosis, and treatment. Malden:Mass.: Blackwell Science, 1999:431-441.
3. Anderson RN. Deaths: leading causes for 2000. *National vital statistics reports.* 2002;50(16):1120-1127.
4. Menon K, Kamath P. Managing the complications of cirrhosis. *May Clin. Proc*. 2000;75(5):501-509.
5. Bosch J, Abraldes JG, Groszmann R. Current management of portal hypertension. *J Hepatol.* 2003;38(Suppl 1):S54-S68.
6. Rimola A, Garcia-Tsao G, Navasa M, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. *J Hepatol.* 2000;32:142-153.
7. Runyon BA, Montano AA, Akriviadis EA, et al. The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. *Ann Intern Med.* 1992;117(3):215-220.
8. Akriviadis EA, Kapnias D, Hadjigavriel M, et al. Serum/ascites albumin gradient: its value as a rational approach to the differential diagnosis of ascites. *Scand J Gastroenterol.* 1996;31(8):814-817.
9. Zhu XH, Liu B, Cheng ZY. Diagnostic value of serum-ascites albumin gradient. *Hunan Yi Ke Da Xue Xue Bao.* 2003;28(3):278-280.
10. Henriksen JH, Parving HH, Christiansen HH, et al. The effect of ascitic fluid hydrostatic pressure on albumin extravasation rate in patients with cirrhosis of the liver. *Scand J Clin Lab*. 1981;41:601-609.
11. Glickman Robert M, Casper D, Braunwald E, et al. In: Harrison's Principles of Internal Medicine. NewYork. Abdominal swelling and ascites., 2005;1:243-5.
12. Gupta R, Mishra SP, Dwivedi M, et al. Diagnosing ascites: Value of ascitic fluid total protein, albumin, cholesterol, their ratios,serum ascites albumin and cholesterol gradient. *Gastroenterol and Hepatol* 1995;10:295-9.
13. Podolsky DK, Isselbacher KJ. Cirrhosis and its complications. In: NewYork Mc Graw Hill publication. 2005;2:1858-68.
14. Sampliner RF, Iber FL. High protein ascites in patients with uncomplicated hepatic cirrhosis. *Am J Med Sci.* 1974;267:275-279.
15. Beg M, Husain S Ahmad, Akhtar N. Serum/Ascites Albumin Gradient in Differential Diagnosis of Ascites. *J Ind Ac Clin Med.* 2001;2(1):511-514.
16. Torres E, Barros P,Calmet F. Correlation between serum-ascites albumin concentration gradient and endoscopic parameters of portal hypertension. *Am J Gastroenter*. 1998;93:2172–2178.
17. Dumont AE, Mulholland JH. Flow rate and composition of thoracic duct lymph in patients with cirrhosis. *N Engl J Med*. 1960;263:471-478.
18. Mayerson HS. The physiologic importance of lymph. In: Handbook of Physiology, Sect.2: Circulation Vol.2, Edited by WF Hamilton. Am. Physiol. Soc., 1963;1035-1073.
19. Orloff MJ, Weight PW, DeBenedetti MJ. Experimental ascites. *Arch Surg.* 1966;93:119-129.
20. Witte CL, Witte MH, Dumont AE, et al. Lymph protein in hepatic cirrhosis and experimental hepatic and portal venous hypertension. *Trans Am Surg Assoc*. 1968;86:256-274.

The Impact of Long Term Medication Ramipril Versus Eprosartane on Renal Function and on Microalbuminuria in Patients with Essential Arterial Hypertension

A. Durnea

Department of Arterial Hypertension, Institute of Cardiology
29/1, N. Testemitanu Street, Chisinau, Republic of Moldova

Corresponding author: +37322256183. E-mail: aliona.durnea@gmail.com
Manuscript received February 17, 2011; revised May 27, 2011

Abstract

This research presents the experience of the Arterial Hypertension Department in the treatment of patients with essential hypertension and microalbuminuria. The study focused on the analysis of clinical observation materials according to the protocol, established in a group of 100 patients, of whom 50 were treated with angiotensin II converting enzyme inhibitors Ramipril and 50 were treated with angiotensin II receptor antagonist Eprosartane. Both drugs have proven beneficial effect on renal function parameters, especially in microalbuminuria at all stages of control with a peak at the end of the follow-up period. However, the treatment with AT1-receptor antagonist Eprosartan has proven to be superior to angiotensin II in converting enzyme inhibitor Ramipril.

Key words: arterial hypertension, microalbuminuria, angiotensin II converting enzyme inhibitors, angiotensin II receptor antagonist.

Влияние рамиприла и эпросартана на функциональное состояние почек у пациентов с гипертонической болезнью и микроальбуминурией при длительном лечении

В статье излагается собственный опыт лечения 100 пациентов с эссенциальной гипертонией и микроальбуминурией на протяжении 12 месяцев. В I-й группе (50 пациентов) принимали ингибитор ангиотензин-превращающего фермента Рамиприл. Во II-й группе (50 пациентов) принимали блокатор рецепторов ангиотензина II Эпросартан. Результаты исследования свидетельствуют о нефропротективной эффективности не только хорошо знакомого ингибитора ангиотензин-превращающего фермента Рамиприла, но и нового блокатора рецепторов ангиотензина II Эпросартан.

Ключевые слова: гипертоническая болезнь, микроальбуминурия, ингибитор ангиотензин-превращающего фермента, блокатор рецепторов ангиотензина II.

Introduction

Arterial hypertension contributes to prognostic worsening depending on the level of subclinical organ damage and on the associated cardiovascular risk factors.

The most recent guideline on hypertension management, elaborated by the European Society of Hypertension in 2009, suggests that "based on recent trial evidence it is recommended to aggressively lower systolic and diastolic blood pressure to values of at least 140/90 mm Hg and lower if tolerated in all patients, and to values less than 130/80 mm Hg in diabetic patients considering the fact that frequently, especially in the elderly it could be difficult to reach values of systolic BP lower than 140 mm Hg" [1].

In general, lowering blood pressure treatment reduces the risk of stroke by 35-40%, for acute myocardial infarction (AMI) by 20-25%, chronic heart failure by 50% and chronic renal failure by 16-26% [2].

Arterial hypertension continues to be a serious issue in modern medicine and clinical trials have proven that through good control of BP values, the rate of cardiovascular events can be significantly reduced. The National Programs for detection and treatment of arterial hypertension have effectively led to the lowering of BP values, in the same time reducing the cardiovascular risk [3].

Chronic renal disease is a frequent complication of arterial hypertension and it favors the elevation of BP values through mechanisms due to renal dysfunction. Arterial hypertension associated with renal dysfunction usually presents great difficulties in treatment.

Kidney damage, even minor (microalbuminuria), has been confirmed as a major negative predictive factor in many diseases. In the mid '80s the first observations were made which associated increased urinary albumine excretion with amplification of cardiovascular morbidity and mortality, both in diabetic patients and hypertensive ones.

Since the first findings, microalbuminuria (MA) was frequently evaluated in big cardiovascular epidemiological trials, becoming also an essential parameter in modern clinical evaluation.

Microalbuminuria in patients with essential arterial hypertension represents a serious problem, associated either with the alteration of vascular hemodynamics or glomerular selectivity, or with the process of initial nephroangiosclerosis or activation of the sympatic nervous system.

Different authors report a microalbuminuria prevalence of 5-10% in the general population, 4.1-40% in patients with essential arterial hypertension and 16-40% in patients with diabetes mellitus. Generally, the presence of MA depends on age, race, body weight and values of blood pressure. It is detected more frequently in black individuals – 14.3%; in those aged < 60 years 6.2%; smokers -1.4%; hypertensive - 35%; obese – 3.6% [4].

Microalbuminuria represents a urinary albumine excretion of 30-300 mg/24 hours or nocturne of 20-200 μg/min. The diagnosis of renal damage induced by arterial hypertension is based on the proof of reduced renal function and /or on the detection of increased urinary albumine excretion.

In the mid '80s, the first trials showed a close relationship between increased urinary albumine excretion, cardiovascular morbidity and mortality both in diabetic and hypertensive patients.

Therefore, considering the importance of the problem, limited data in the specialty literature that would reflect the renal protection effects of a new angiotensin II receptor antagonist – Eprosartane, we have proposed the initiation of a prospective, randomized trial which would compare this drug to a well-studied angiotensin II - converting enzyme inhibitor – Ramipril.

The aim of the study

The evaluation of the action of long-term antihypertensive medication of angiotensin II – converting enzyme inhibitor Ramipril versus angiotensin II receptor antagonist Eprosartane on the renal function and microalbuminuria.

Material and methods

One hundred subjects were included in the trial (48 men, 52 women), mean age 51.1 ± 0.86 years with essential arterial hypertension of II-III grade and microalbuminuria, without associated clinical conditions. After registration and the primary visit the patients signed an informed consent form in order to participate in the trial. All antihypertensive drugs administered before have been suspended for a three week period. After the end of this period the patients came for the second visit to measure BP and to confirm the presence of BP values ≥ 160/90 mm Hg.

According to the study protocol the patients were divided randomly in two groups:

I group (50 patients) administered angiotensin II - converting enzyme inhibitor – Ramipril in the mean dose (15.3 ± 1.2 mg/day) + indapamide 2.5 mg/day.

II group (50 patients) administered angiotensin II receptor antagonist – Eprosartane in the mean dose (850 ± 12.4 mg/day) + indapamide 2.5 mg/day.

The renal excretory function has been evaluated through plasmatic urea, serum creatinine, glomerular filtration rate and microalbuminuria.

The patients were examined and treated in the clinic of Institute of Cardiology during 2007-2010. The observation period lasted 12 months with evaluations in dynamics at 3, 6, 9 and 12 months.

Results

The determination of renal excretory function is essential for the diagnosis of renal failure. Also, exact knowledge of renal excretory capacity is indispensable for the determination of doses of drugs, in order to avoid potential accidents related to overdoses.

In initial stage the groups were comparable. In this way, serum urea varied in the range 2.7 - 19 mmol/l (mean 7.0 ± 0.45 mmol/l) in group I and 3.8 – 14.9 mmol/l (mean 5.8 ± 0.29 mmol/l) in group II, plasmatic creatinine varied in the range 50.1 – 296.7 mmol/l (mean 98.3 ± 5.34 mmol/l) in group I and, respectively, 50.1-271.4 mmol/l (mean 88.5 ± 4.11 mmol/l) in group II.

The glomerular filtration rate was in the range 67.3 – 115.3 ml/min (mean 87.2 ± 4.17ml/min) in group I and, respectively, 69.3 – 111.3 ml/min (mean 94.5 ± 3.34ml/min) in group II ($p < 0.05$).

Table 1

Parameters of renal function in the initial stage, (M ± m)

Groups	PU (mmol/l)	SC (mmol/l)	GFR (ml/min)	MA (µg/min)	p
I - Ramipril	7.0±0.45	98.3±5.34	87.2±4.17	73.1±5.52	< 0.05
II - Eprosartane	6.8±0.29	88.5±4.11	94.5±3.39	68.1±4.16	< 0.05

Abbreviations: PU – plasmatic urea; SC – serum creatinine; GFR – glomerular filtration rate; MA – microalbuminuria.

The microalbuminuria grade, which shows the presence of significant endothelial dysfunction, was also comparable in initial stage in both groups: in the range 35.7 – 98.6 µg/min (mean 73.1 ± 5.52 µg/min) in group I and, respectively, 40.3 – 93.1 µg/min (mean 68.1 ± 4.16 µg/min in group II $p < 0.05$) (tab. 1).

After 3 months of medication, plasmatic urea (mmol/l) was reduced by 11.4% (from 7.0 ± 0.45 to 6.2 ± 0.41) ($p > 0.05$) in group I and 20.5% (from 6.8 ± 0.29 to 5.4.± 0.18) ($p < 0.05$) in group II; after 6 months in group I by 14.2% (from 7.0 ± 0.45 to 6.0 ± 0.27) ($p < 0.05$) versus 19.1% (from 6.8 ± 0.29 to 5.5 ± 0.16) ($p < 0.05$) in group II; after 9 months by 21.4% (from 7.0 ± 0.45 to 5.5 ± 0.2) ($p > 0.05$) in group I and 23.5% (from 6.8 ± 0.29 to 5.2 ± 2.2) ($p > 0.05$) in group II and after 12 months of observation by 15.7% ($p < 0.05$) and 26.4% ($p < 0.05$) respectively (fig. 1).

Serum creatinine (mmol/l) after 3 months of medication reduced nonsignificantly by 2% (from 98.3 ± 5.3 to 96.3 ± 6.5) in patients receiving Ramipril and statisticaly authentic – by 15.1% (from 96.5 ± 4.1 to 81.9 ± 2.2) ($p < 0.05$) using Eprosartane.

This trend became statistically authentic from 6 months of medication on, but more evident with the administration of Eprosartane, the peak being reached to the end of 12 months of medication – 9.5% group I versus 18.5% group II, respectively (fig. 2).

The glomerular filtration rate decreased nonsignificantly in both therapeutic schemes after 3 months of medication – about 2%. This became statistically authentic from 6 months of medication on, but more evident with the administration of Eprosartane, the peak being reached at the end of 12 months of medication – 31.4% group I versus 22.1% group II. The reduction of renal flow is a normal connotation of systemic blood pressure, however, the absolute values of glomerular filtration rate didn't pass above normal after medication (fig. 3).

The values of microalbuminuria had an impressive evolution. The 3 month-long treatment with Ramipril or Eprosartane resulted in a comparable reduction, statistically authentic, of microalbuminuria – by 67% and 65% ($p < 0.05$), respectively. This was revealed at 6, 9 and 12 months of ob-

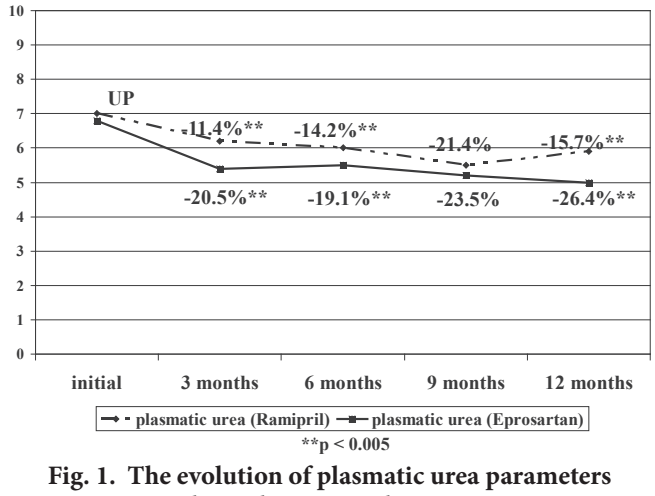

Fig. 1. The evolution of plasmatic urea parameters depending on medication.

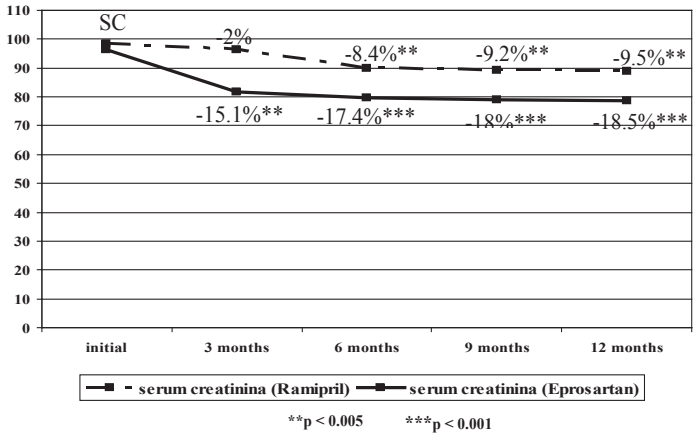

Fig. 2. The evolution of serum creatinine parameters depending on medication.

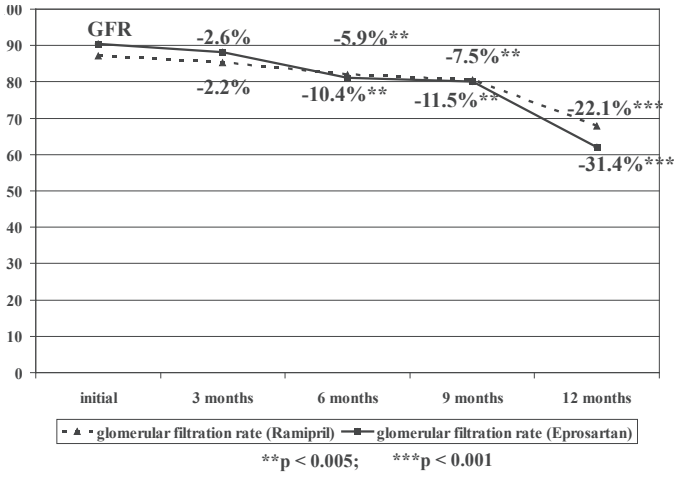

Fig. 3. The evolution of glomerular filtration rate parameters depending on medication.

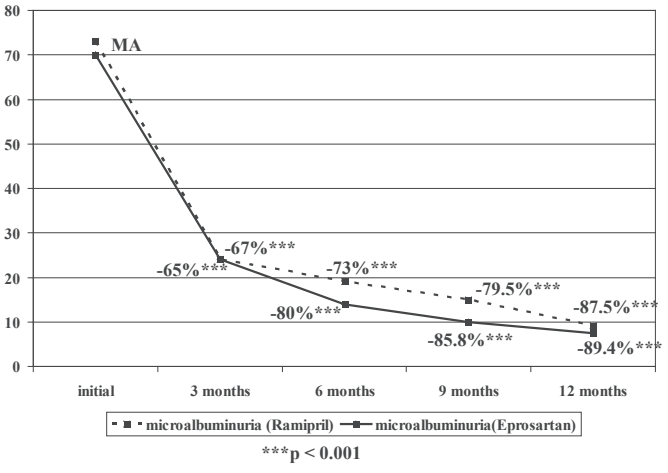

Fig. 4. The evolution of microalbuminuria parameters depending on medication.

servation. At the end of the observation period the values of microalbuminuria reached normality (< 20μg/min) in all subjects treated with Eprosartane, having average values of 7.4±1.2 which represents a difference of 89.4% compared to initial ($p < 0.001$) (fig. 4).

Ramipril has also been efficient, but a little more modestly, the average reduction compared to initial being of 87.5% (from 73.1 ± 5.5 μg/min to 9.1 ± 1.4 μg/min). Concomitantly in 5 patients from group I the values of MA passed nonsignificantly the normal target value.

Generally, the presence of proteinuria in the daytime at initial stage was detected in 43 (86%) patients from group I and 40 (80%) from group II. Long-term treatment with Ramipril or Eprosartane resulted in an important reduction of the number of patients with proteinuria.

Therefore, after 3 months of treatment the number of these patients decreased more than 2-fold in both groups, and after 6 months 4.3-fold at Ramipril administration and "sic" 8-fold using Eprosartane. To the end of the trial the percent of patients with proteinuria reduced from 43% to 4% in the group treated with Ramipril and from 40% to 2% in those treated with Eprosartane (tab. 2).

Table 2

The prevalence of patients with proteinuria (Nr; %)

Group	Initial	3 months	6 months	9 months	12 months
I group (Ramipril)	43 (86%)	19 (38%)	10 (20%)	4 (8%)	2 (4%)
II group (Eprosartane)	40 (80%)	18 (36%)	5 (10%)	3 (6%)	1 (2%)

Recapitulating, the administration of angiotensin II - converting enzyme inhibitor Ramipril, as well of angiotensin II receptor antagonist Eprosartane did not have a negative impact on renal function. It can be mentioned even a reduction of blood nitrogen evaluated through ureea and serum creatinine, despite of the reduction of glomerular filtration. The decrease, while nonsignificant of the renal flow, can be explained by efficient reduction of systolic blood pressure.

The greatest connotation is due to the normalization in all patients of the values of microalbuminuria at the administration of Eprosartane and reduction to normality in 90% of the ones treated with Ramipril.

Discussion

Almost 50 years have passed since arterial hypertension has been defined as cardiovascular risk factor for the systolic and diastolic values. The rate of cardiovascular events raises concomitantly with systolic BP at any age, but the correlation of diastolic BP and cardiovascular mortality is directly proportional only until the age of 50, and inversely proportional after the age of 60 [5].

Numerous randomized placebo-controlled trials have investigated the benefit of the lowering of blood pressure using different groups of antihypertensive drugs.

A similar approach was used in order to study new ARB II drugs. In SCOPE trial, in elderly patients (of more than 70 years), candesartane which was often associated with a diuretic, reduced BP versus placebo with 3.2/1.6 mm Hg, noting a significant reduction of the non-fatal stroke incidence. In RENAAL and IDNT trials in hypertensive patients with diabetes mellitus and diabetic nephropathy, the adding of ARB II losartane or irbesartane led to a significant reduction of cardiovascular morbidity [6, 7].

In MOSES trial (hypertensive patients with supported anterior cerebrovascular event) a comparison was performed between medications with eprosartane vs calcium blocker nitrendipine. During 2.5 years of observation, significantly less strokes (31%) were noted in patients treated with eprosartane in conditions of a similar decrease in BP values [8].

Present data confirm the impact of proteinuria, which is a marker of endothelial dysfunction, on general and cardiovascular morbidity.

In this way, Culleton and al. have examined the elderly population included in Framingham trial in the perspective of analysis of the association between proteinuria and the incidence of coronary artery disease, cardiovascular and general mortality. According to the data on other cardiovascular risk

factors, including elevation of serum creatinine, after 17 years of clinical studies proteinuria represented a risk factor for general mortality among the male and female population, the death risk being ampified 1.3 to 2.6 fold because of increased urinary protein excretion [9].

The importance of proteinuria as a risk factor has been studied in another even greater trial MRFIT. After 6 years of observation the presence of proteinuria has been significantly and independently associated with general, cardiovascular and coronary artery disease mortality, the risk raising with the level of proteinuria [10].

The importance of proteinuria in cardiovascular morbidity and mortality is deducted indirectly in the HOPE trial. Treatment with ramipril decreased the risk for acute myocardial infarction by 22%, for stroke by 33%, cardiovascular mortality by 37% and general mortality by 24%. The risk for occurrence of clinically manifest diabetic nephropathy reduced by 24%. These effects were independent from the antihypertensive effect of ramipril. The authors concluded that ramipril has an important vascular and renal protective effect [11].

Normaly, a minimum quantity of proteins with a mean of 80 mg/day is being excreted with urine, 15% of which are albumines. Therefore, proteinuria is defined as an urinary protein excretion of more than 0.3 g in urine in 24 hours. In case of febrile disease, urinary infection or excessive effort, proteinuria may become periodicaly significant, without a particular long term importance.

The proteins in normal and pathological urine are generated from three major sources:

- plasmatic proteins filtrated physiologicaly or pathologicaly by glomerular capilars and that avoids reabsorbtion at the level of proximal renal tubes;
- proteins secreted physiologicaly by tubular cells (for example, Tamm-Horsfall protein) or lost in the tubular lumenum because of tubular damage;
- proteins secreted by cells or glands in inferior urinary tract or proteines resulted from inflamation of the urinary tract.

In our study the presence of mild proteinuria (< 1g/24h) in initial stage has been observed in 86% patients in the group treated with Ramipril and 80% with eprosartane. The long-term medication resulted in important reduction of the number of patients with proteinuria.

Therefore, after 3 months of treatment the number of these patients diminished more than 2-fold in both groups, and after 6 months 4.3-fold during Ramipril administration and "sic" 8-fold using Eprosartane. At the end of the trial, the percent of patients with proteinuria reduced from 43% to 4% in the group treated with Ramipril and from 40% to 2% in those treated with Eprosartane. In this way, we can conclude that ARB II Eprosartane has a renoprotective effect through reduction of proteinuria.

It is known the fact that microalbuminuria represents a high cardiovascular and renal risk factor compared to subjects with "normal" urinary excretion (< 30 mg/24h). In MONICA trial it was demonstrated that microalbuminuria in hypertension represents an important and independent cardiovascular risk factor. The presence of microalbuminuria in these patients correlates with a greater prevalence and severity of left ventricular hypertrophy, hypertensive retinopathy, "non-dipping" hypertension and carotid arteriosclerosis [12].

In Groningen trial, a doubling of urinary albumine concentration was associated with an increase by 29% of cardiovascular mortality and by 12% of noncardiovascular mortality. There is evidence that microalbuminuria is a marker not only for endothelial dysfunction in glomerules, but also in the whole vascular system[13].

In those 100 patients with moderate-to-severe hypertension included in our trial, the presence of microalbuminuria was mandatory and it constituted: 73.1 ± 5.52 μg/min in the group treated with Ramipril and 68.1 ± 4.15 μg/min with Eprosartane ($p < 0.05$). The mean values of glomerular filtration rate were within normal limits 87.2 ± 4.17 ml/min in the group treated with Ramipril and 94.5 ± 3.34 ml/min in the group treated with Eprosartane ($p < 0.05$). Therefore, in the case of our trial it can be also firmly said that the presence of microalbuminuria confirms the fact that there were patients included with important vascular damage.

On antihypertensive treatment Ramipril versus Eprosartane in our trial the values of microalbuminuria had an impressive evolution. Only 3 months of medication resulted in a statisticaly significant reduction from initial microalbuminuria 67% on Ramipril and 65% on Eprosartane ($p < 0.05$). At the end of the observation period (12 months) the level of microalbuminuria reached the norm limit (< 20 μg/min) in all subjects treated with Eprosartane, forming a difference of 89.4% compared to the initial ($p < 0.001$). Ramipril was a little more modest, the decrease of microalbuminuria being of 87.5% compared to the initial, concomitantly in 10% of patients the values MA passed nonsignificantly the normal target value.

Despite of the absence of survival benefits, these data prove the necesity of use of ACE II or ARB II in hypertensive patients with high risk and chronic renal disease.

Conclusions

1. Microalbuminuria represents an independent and important cardiovascular risk factor in general population, diabetic and hypertensive, being a marker of generalized vascular dysfunction.

2. The presence of proteinuria has to lead not only to detailed kidney investigations for the detection of the etiology of renal damage, but also to cardiologic exploration, evaluation of cardiovascular risk, as well as aggressive treatment.

3. Serious renoprotective effect (important reduction of microalbuminuria) is installed in 6 months from initiation of medication with Ramipril or Eprosartane. Continuation of medication induces progressive reduction of microalbuminuria, superior efficiency being found at the administration of angiotensin II receptor antagonist Eprosartane.

4. The administration of angiotensin II receptor antagonist

Eprosartane, in the presence of contraindications for angiotensin II - converting enzyme inhibitor Ramipril, is absolutely opportune in the presence of hypertensive microalbuminuria.

References

1. Mancia G, De Backer G, Dominiczak A, et al. 2009 ESH-ESC Guidelines Managment of arterial Hypertension. *J. Hypertens*. 2009;25:1105-1188.
2. Stevens LA, Caresh J, Greene T, et al. Assessing kidney function-measured and estimated glomerular filtration rate. *N Engl J Med.* 2006;354:2473-2483.
3. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC report. *JAMA*. 2007;289:2560-2572.
4. Stevens LA, Caresh J, Greene T, et al. Assessing kidney function-measured and estimated glomerular filtration rate. *N Engl J Med*. 2006;354:2473-2483.
5. Franklin SS, Larson MG, Khan SA, et al. Does the relation of blood pressure to coronary heart risk change with aging? *Circulation*. 2001;103:1245-1249.
6. Zeeuw de D, Remuzzi G, Parving HH, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. *Kidney Int*. 2004;65:2309-2320.
7. American Diabetes Association: Diabetic nephropathy. *Diabetes Care*. 2002;25(Suppl 1):585-589.
8. Schrader J, Luders S, Kulschewski A, et al. MOSES Study Group. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke*. 2005;36(6):1218-26.
9. Culleton BF, Larson MG, Parfrey PS, et al. Proteinuria as a risk factor for cardiovascular disease and mortality in older people: a prospective study. *Am J Med*. 2000;109:1-8.
10. Grimm RH, Svendsen KH, Kasiske B, et al. Proteinuria is a risk factor for mortality over 10 years of follow-up. MRFIT Reserch Group. Multiple Risk Factor Intervention Trial. *Kidney Int Suppl*. 1997;63:S10-4.
11. HOPE investigators. Effects of angiotensin-converting-enzime, ramipril, on cardiovascular events in hight-risk patients. *N Engl J Med*. 2000;342:145-53.
12. Ruilope LM, Rodicio JL. Clinical relevance of proteinuria and microalbuminuria. *Curr Opin Nephrol Hypertens*. 1993;2:962-7.
13. Jong de PE, Hillege HL, Pinto-Sietsma SJ, et al. Screening for microalbuminuria in the general population: a tool to detect subjects at risk for progressive renal failure in an early phase? *Nephrol Dial Transplant*. 2003;18:10-13.

Cathepsin D Activity in Experimental Liver Chirrosis and After the Administration of Copper Coordination Compounds and Bacterian Remedy BioR

O. Tagadiuc*, V. Rivneac, V. Gudumac, E. Rivneac, L. Andronache, V. Sardari

Laboratory of Biochemistry, Nicolae Testemitanu State Medical and Pharmaceutical University
165, Stefan cel Mare Street, Chisinau, Republic of Moldova

*Corresponding author: +37322205136. E-mail: olgatagadiuc@gmail.com

Manuscript received March 11, 2011; revised June 04, 2011

Abstract

This paper investigates the influence of the copper coordination compounds CMT-28, CMT-67 and of the bacterial remedy BioR on the cathepsin D activity in liver in experimental cirrhosis. The activity of cathepsin D was also detected electron-histochemicaly in the liver during the regression of experimental hepatic cirrhosis. The result suggests that the coordinative compound CMT-67 used in combination with the bacterial remedy BioR has a pronounced stimulating effect on the enzymatic hydrolysis of the extracellular matrix under the action of cathepsin D and contributes to a more efficient breakdown of the excessive fibrous tissue in liver. It was determined that the active cathepsin D is localized intracellularly in the lysosomes of hepatocytes, macrophages, fibroblasts and endothelial cells, as well as extracellularly on the collagen fibrils near the parenchymal and mezenchymal cells. In addition to its participation in the intracellular proteolysis, cathepsin D is secreted by the hepatocytes and connective tissue cells to the extra-cellular space and participates in the extracellular breakdown of the fibrous tissue.

Key words: cathepsin D, liver cirrhosis, coordinative compounds of cuprum, bacterial remedy BioR.

Активность катепсина D при экспериментальном циррозе печени и при введении координационных соединений меди и препарата бактериального происхождения BioR

Было изучено влияние координационных соединений меди CMT-28, CMT-67 и препарата бактериального происхождения BioR на активность катепсина D в печени при экспериментальном циррозе. Активность катепсина D была также выявлена электронно-гистохимически в печени при регрессии экспериментального цирроза. Результаты свидетельствуют о том, что координационное соединение меди CMT-67, введенное в комбинации с препаратом бактериального происхождения BioR, имеет выраженное стимулирующее влияние на ферментативный гидролиз внеклеточного матрикса под влиянием катепсина D и способствует более эффективному распаду фиброзной ткани в печени.