A bystander effect in hypertension: left ventricular hypertrophy, microalbuminuria, and diabetes mellitus

Catalina Arsenescu-Georgescu[1,2], Delia Lidia Salaru[1,2]

[1] Institute of Cardiovascular Diseases "Prof. Dr. George I.M. Georgescu"
[2] University of Medicine and Pharmacy "Gr. T. Popa" Iaşi

Abstract

Even though the clinical research progressed during the last years regarding the different mechanisms involved in the occurrence and progression of hypertension, new results are needed in order to adopt clinically efficient strategies of prevention and treatment. Microalbuminuria and left ventricular hypertrophy (LVH) reflect different aspects of the cardiovascular impairment, being either causes or consequences of the target organ damage in hypertension. In the present study we aimed to investigate the correlation between microalbuminuria and left ventricular hypertrophy, as target organ damage, and diabetes mellitus in a population of hypertensives with or without established coronary disease.

157 hypertensive patients were included in the study and they were screened for microalbuminuria. A first-morning urine sample was analysed by immunoturbidimetry and values between 20–200 mg/l accounted for microalbuminuria. Left ventricular hypertrophy (LVH) was assessed by echocardiography by a single investigator.

51.6% of the study population had microalbuminuria, without significant prevalence rates between the group with DM (46.3%) and without DM (54.4%). Patients with DM were younger and mostly male. They were more likely to be smokers, dyslipidemic, and obese. Compared to subjects without DM, hypertensives with DM had a greater prevalence of LVH (59.3% *versus* 42.7%, p=0.049) and higher values of albuminuria (mean 39.9 mg/l *versus* 26.8 mg/l, p=0.016). In patients with diabetes mellitus, there is a significant correlation between microalbuminuric and non-microalbuminuric patients according to left ventricular hypertrophy, p=0.001.

Our findings highlight the need to address hypertension as a complex healthcare problem and to routinely determine target organ damage, especially in diabetic patients.

Keywords: microalbuminuria, left ventricular hypertrophy, diabetes mellitus.

Introduction

Despite extensive research and debate there is still not a unitary mechanism – and consequently not only a single therapeutic target – for hypertension. Its orchestration is assured by numerous influences and implies neural, renal, hormonal, vascular structures. The physiopathology of hypertension involves a complex interaction of vascular effectors, such as cathecolamines, renin-angiotensin system, oxidative stress, nitric oxide, vascular endothelial growth factor, endothelin-1 and several inflammatory cytokines. There is still an active search for new methods to approach diagnosis, therapy and prevention of this disease [1]. Even though the clinical research progressed during the last years regarding the different mechanisms involved in the occurrence and progression of hypertension, new results

* Correspondence to: Dr. Catalina Arsenescu-Georgescu, Delia Lidia Salaru, Institute of Cardiovascular Diseases "Prof. Dr. George I.M. Georgescu", University of Medicine and Pharmacy "Gr. T. Popa" Iasi

are needed in order to adopt clinically efficient strategies of prevention and treatment.

Both in hypertensive diabetic and non-diabetic patients, microalbuminuria, even below conventional threshold, has proven a predictor of cardiovascular events and several studies reported a continuous relationship between cardiovascular and non-cardiovascular mortality and urinary albumin/creatinine ratio ≥3.9 mg/g in men and 7.5 mg/g in women. Microalbuminuria was further associated with hypertension in non-diabetic individuals, and lately it become an independent risk factor for cardiovascular disease, increasing all-cause mortality in non-specific population, in women at menopause, elderly, diabetics, hypertensives with or without diabetes mellitus [2–6].

Microalbuminuria and left ventricular hypertrophy (LVH) reflect different aspects of the cardiovascular impairment, being either causes or consequences of the target organ damage in hypertension. The assumptions are that microalbuminuria and LVH, as target organs, mirror the severity and complications of hypertension or that are simply the results of a common pathological way. In any case, the physiopathological mechanisms that determine the evolution from LVH to a cardiovascular event is still unclear, but it could rely on the accelerated atherosclerosis due to systemic inflammation and endothelial dysfunction.

Even though several trials suggested that microalbuminuria is associated with some cardiovascular risk factors like age, male gender, hypertension, diabetes, smoking, obesity, and dyslipidemia, it is obvious that it only explains a minor part of the association between microalbuminuria and atherosclerotic events. It could be an inadequate quantification of these factors or there could others that could cause microalbuminuria and associated cardiovascular disease.

In the present study we aimed to investigate the correlation between microalbuminuria and left ventricular hypertrophy, as target organ damage, and diabetes mellitus in a population of hypertensives with or without established coronary disease.

Methods

Patients

157 hypertensive patients admitted in the Institute of Cardiovascular Diseases from January 2012 to December 2013 were included in the study and they were screened for microalbuminuria. Exclusion criteria were represented by fever (> 38°C), chronic kidney disease (eGFR <60 ml/min/1,73 m^2, Cockroft-Gault formula), urinary tract infection or extensive physical effort 24 h prior to the measurement. All patients gave written informed consent for participating in the study. The study was in accordance with the ethical principles of the Declaration of Helsinki and was approved by the local ethics committee.

Study design and procedures

Collected baseline data of the patients included medical history, demographics, biometric data, urine and blood collections, and laboratory analysis. A first-morning urine sample was analysed by immunoturbidimetry and values between 20–200 mg/l accounted for microalbuminuria. Patients with urinary albumin excretion >200 mg/l were excluded. Patients with values <20 mg/l were considered normoalbuminuric. For statistical purposes, the patients were divided into two groups: with diabetes mellitus (DM) – 54 patients, and without DM – 103 patients.

Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure > 90 mmHg, and/or use of antihypertensive drugs. Dyslipidemia was defined as cholesterol > 180 mg/dl and/or HDL < 40 mg/dl in male patients and < 50 mg/dl in female patients and/or LDL > 160 mg/dl and/or triglycerides > 150 mg/dl and/or use of lipid-lowering treatment. Obesity was defined as BMI >= 30 kg/m^2. Diabetes was defined as fasting plasma glucose levels > 126 mg/dl and/or use of antidiabetic therapy. The diagnosis of coronary artery disease was based on the medical history, clinical and biochemical assessement, as well as diagnostic procedures (coronarography).

Left ventricular hypertrophy (LVH) and left ventricular ejection fraction (LVEF) were assessed by echocardiography by a single investigator. LVH was defined as posterior wall thickness or/and interventricular septum thickness > 12 mm (M-Mode measurement). Left ventricular ejection fraction (LVEF) was determined using the Simpson method.

Statistical methods

Results are presented as mean ± SD or median (interquartile range) for continuous variables and as percentages of the total number of patients for categorical variables. Correlation analysis were conducted using Pearson (r) or Spearman (ρ) tests. The data were also logarithmically transformed to achieve normal distribution, whenever possible. We performed univariate analysis using a t-test for normally distributed continuous variables and Mann-Whitney test if variables were not normally distributed. Comparisons of categorical variables were analyzed by the Chi-square test. A P value ≤ 0,05 was considered significant. Statistical analysis was performed with SPSS 20.0 (SPSS Inc., Chicago, IL,USA).

Results

The baseline characteristics of all patients with and without diabetes are shown in Table 1. The mean age of the 157 subjects was 65.9 years, 44.6% were male. 51.6% of the study population had microalbuminuria, without significant prevalence rates between the group with DM (46.3%) and without DM (54.4%).

Patients with DM were younger and mostly male. They were more likely to be smokers, dyslipidemic, and obese, in

Table 1. Baseline characteristics of the study population

Clinical and biochemical parameters	TOTAL (157)		Without DM (103)		With DM (54)		P value
	%	Mean	%	Mean	%	Mean	
Creatinine (mg/dl)		0.9 (0.87 - .92)		0.87 (0.84 - 0.90)		0.95 (0.91 - 0.99)	0.001
LDL-Chol (mg/dl)		116.75 (111.32 - 122.17)		112.5 (106.54 - 118.45)		124.85 (113.93 - 135.78)	0.032
Glycemia (mg/dl)		134.80 (124.24 - 145.37)		100.5 (98.59 - 102.38)		200.3 (178.44 - 222.08)	0.000
TG (mg/dl)		152.46 (140.71 - 164.21)		142.87 (129.79 - 155.96)		170.74 (147.58 - 193.9)	0.039
TChol (mg/dl)		189.66 (183.5 - 195.82)		186.47 (179.77 - 193.16)		195.74 (183 - 208.48)	0.158
MAU (mg/l)		31.29 (26.17 - 36.42)		26.8 (21.71 - 31.83)		39.9 (28.7 - 51.2)	0.016
HDL-Chol (mg/dl)		49.01 (47.33 - 50.68)		50.14 (48.13 - 52.14)		46.85 (43.83 - 49.87)	0.073
Age, y		65.93 (64.21 - 67.65)		66.8 (64.6 - 69.02)		64.3 (61.52 - 67)	0.166
Male	44.6%		40.8%		51.9%		0.185
Smokers	37.6%		28.2%		55.6%		0.001
MAU, %	51.6%		54.4%		46.3%		0.336
Dyslipid	74.5%		70.9%		81.5%		0.147
Obese	31.8%		17.5%		59.3%		0.000
LVH present	48.4%		42.7%		59.3%		0.049
CAD present	69.4%		56.3%		94.4%		0.000

TChol, Total cholesterol; LDL-chol, LDL-cholesterol; HDL-chol, HDL-cholesterol; TG, triglycerides; MAU, microalbuminuria, LVH, left ventricular hypertrophy; CAD, coronary artery disease.

Table 2. Distribution of patients with LVH according to the presence of MAU and DM

				LVH							
				Without LVH				With LVH			
				No. of patients	Row N %	Layer N %	Column N %	No. of patients	Row N %	Layer N %	Column N %
DM	0	MAU	0	31	66.0%	19.7%	52.5%	16	34.0%	10.2%	36.4%
			1	28	50.0%	17.8%	47.5%	28	50.0%	17.8%	63.6%
	1	MAU	0	18	62.1%	11.5%	81.8%	11	37.9%	7.0%	34.4%
			1	4	16.0%	2.5%	18.2%	21	84.0%	13.4%	65.6%

statistically significant percentages. Compared to subjects without DM, hypertensives with DM had a greater prevalence of LVH (59.3% *versus* 42.7%, p=0.049) and higher values of albuminuria (mean 39.9 mg/l *versus* 26.8 mg/l, p=0.016). The proportion of normoalbuminuric and microalbuminuric patients did not differ between subjects with or without DM. A significant number of patients with DM also had coronary artery disease.

In a univariable linear regression, microalbuminuria positively correlated with the presence of coronary artery disease (β = 0.194±0.001, p=0.015) and LVH (β = 0.311±0.001, p<0.001). A total of 60.5% of subjects with microalbuminuria also had LVH.

A further logistic regression showed that increasing albuminuria rates influences the presence or absence of LVH [Exp(B)=1.025, p=0.001], and the presence or absence of CAD [Exp(B) =1.019, p=0.023].

Table 2 represents a contingency table for the distribution of cases with LVH. 66% of the patients without DM do not have microalbuminuria, nor left ventricular hypertrophy. 17.8% of the patients without DM, have microalbuminuria and do not have LVH. 18.2% of the patients with DM have microalbuminuria, but do not have LVH.

Chi-square tests reveal that there are no significant differences between patients with or without microalbuminuria categorised by the presence of left ventricular hypertrophy in patients without diabetes mellitus, p=0.103. In patients with diabetes mellitus, there is a significant correlation between microalbuminuric and non-microalbuminuric patients according to left ventricular hypertrophy, p=0.001.

Discussion

We have observed a very high prevalence rate for microalbuminuria in the study population, more than 50% of subjects having albuminuria values between 20–200 mg/l. The other cardiovascular risk factors are well represented, with a high prevalence of dyslipidemia. All in all there is a population at high cardiovascular risk, 109 out of 157 patients already having coronary artery disease. Even if there are no differences in the percentages of normoalbuminuric and microalbuminuric subjects between the two groups with/without DM, there is a tendency towards increasing values of microalbum inuria in the DM group.

Cardiovascular morbidity and mortality is a major burden in hypertensive patients with type 2 diabetes, particularly if micro- and macroalbuminuria is present. This study shows that the abundance of cardiovascular risk factors, when taking into consideration both traditional factors and the markers of target organ damage, leads to a high-risk profile of the hypertensive patient. The likelihood of a subsequent coronary artery disease is very high. The add-on risk of left ventricular hypertrophy and microalbuminuria was clearly defined.

Two important issues are already known about microalbuminuria: first, prevention of albuminuria development is a reachable objective in patients with hypertension and diabetes, and secondly, lowering albumin excretion was followed by a significant decrease of cardiovascular events and death. This data strengthen the need to improve knowledge about the predictors and evolution of microalbuminuria. Progression towards macroalbuminuria appears in a significant number of cases, especially in diabetics, but not only, indicating the presence of renal disease. This progression can also be observed in patients with hypertension, but also with advanced cardiovascular disease [7].

Increased glomerular albumin passage occurs due to functional (physiological - reversible) and structural (pathological - irreversible) changes such as: elevated glomerular hydraulic pressure, increased glomerular filtration coefficient, change in size and charge selectivity of the glomerular membrane [8, 9]. Diabetes and hypertension can induce abnormalities in all the three distinct layers of the glomerular membrane - endothelial cell layer, basement membrane and podocyte layer.

The mechanisms linking microalbuminuria with fatal and nonfatal cardiovascular disease remain poorly understood [10]. Microalbuminuria has been suggested as a marker of widespread endothelial dysfunction that might predispose to increased penetration in the arterial wall of atherogenic lipoprotein particles (the Steno hypothesis) [11]. Second, microalbuminuria has been suggested simply as a marker of established vascular disease. Thirdly, microalbuminuria is associated with excess of well-known cardiovascular risk factors such as: elevated blood pressure, dyslipoproteinaemia, enhanced platelet aggregation, insulin resistance and autonomic neuropathy [12–17].

In PREVEND, doubling of microalbuminuria associated with an increase with 29% of cardiovascular death, with a permanent correlation between increased microalbuminuria and cardiovascular diseases, and the microalbuminuria value from the first measurement remained a constant predictor of cardiac events even after 5 years of follow-up [18].

Both proteinuria and insulin resistance were associated with atherogenesis. The study Insulin Resistance Atherosclerosis which included 982 non-diabetic participants showed that the subjects with microalbuminuria had a diminished sensibility to insulin and higher plasmatic insulin levels when compared to normoalbuminuric participants, which determined the authors to conclude that insulin resistance plays a role in increasing the cardiovascular risk conferred by proteinuria [19]. Hyperinsulinemia was demonstrated to induce renal vasodilation and increased glomerular filtration rate in mice, suggesting that this localised high pressure could be involved in the adjustment of albumin excretion rate.

Due to the importance of subclinical organ damage as an intermediate stage in the continuum of the vascular damage and as one of the determinants of the global cardiovascular risk, the signs of organ damage should be carefully looked for. There is increasing evidence suggesting it has a crucial role in assessing the cardiovascular risk in individuals with or without hypertension.

The association between microalbuminuria and LVH, left ventricular dysfunction and electrocardiographic abnomalities has been demonstrated in several studies [20–22]. In LIFE study, in hypertensive patients with electrocardiographic sign of LVH, the abnormal geometry of left ventricle and increased left ventricular mass have been correlated with urinary albumin excretion irrespective of age, systolic arterial pressure, diabetes, and race, suggesting the parallel between cardiac and microvascular damage [23].

Even though microalbuminuria and left ventricular mass are significantly and independently correlated, determining microalbuminuria might bring additional information in the assessment of cardiovascular risk beyond the ecocardiographic detection of left ventricular hypertrophy. In a group of 312 hypertensive patients it has been observed that the intensive investigation of subclinical organ damage, including microalbuminuria and the ecocardiographic evaluation of LVH, increases the proportion of patients that should be placed in a higher absolute risk category. Overall, 26% of these patients moved to a higher risk scale, and this proportion was significantly higher than the number of reclassified patients after determining only microalbuminuria (14%) or LVH (16%) [24].

Our study underlines exactly this multiplication of the cardiovascular risk in hypertensive patients, showing

that it is clinically relevant to take into consideration more parameters, including markers of organ damage.

Hypertensives with other risk factors – smoking or dyslipidemia – and microalbuminuria had a greater organ damage, with a 50% higher risk than patients without microalbuminuria. This marks the need for intensified treatment with multifactorial intervention targeting glycaemic control, blood pressure including blockade of the renin angiotensin system, and treatment of dyslipidaemia [25].

Owing to the importance of asymptomatic organ damage as an intermediate stage in the continuum of vascular disease, and as a determinant of overall cardiovascular risk, the European Guidelines for the Management of Hypertension underline the crucial role of organ damage in determining the cardiovascular risk of individuals with and without high blood pressure [26]. The observation that any of the four markers of organ damage (microalbuminuria, increased pulse wave velocity, left ventricular hypertrophy and carotid plaques) can predict cardiovascular mortality independently of SCORE stratification is a relevant argument in favor of using assessement of organ damage in daily clinical practice [27].

Conclusions

Our findings highlight the need to address hypertension as a complex healthcare problem and to routinely determine target organ damage, especially in diabetic patients. Microalbuminuria is associated with a higher prevalence of diabetic complications, metabolic and non-metabolic risk factors, subclinical organ damage as well as adverse cardiovascular events in both diabetic and non-diabetic people with essential hypertension. Given its importance as a strong, early and independent marker of increased cardiovascular risk in hypertension, these results mandate more rigorous screening of microalbuminuria, as well as of left ventricular hypertrophy, in the hypertensive population and successful strategies will likely require more aggressive action towards its treatment.

Conflict of interest

The authors confirm that there are no conflicts of interest.

References

1. Kaplan NM, Victor RG. Kaplan's Clinical Hypertension, Tenth Edition. Wolters Kluwer, Lippincott Williams& Wilkins, 2010, 3, 42-107
2. Roest M, Banga JD, Janssen WM, Grobbee DE, Sixma JJ, de Jong PE, *et al.* Excessive urinary albumin levels are associated with future cardiovascular mortality in postmenopausal women. *Circulation.* 2001;103:3057-61.
3. Damsgaard EM, Froland A, Jorgensen OD, Mogensen CE. Microalbuminuria as predictor of increased mortality in elderly people. *BMJ.* 1990;300:297-300.
4. Agewall S, Wikstrand J, Ljungman S, Fagerberg B. Usefulness of microalbuminuria in predicting cardiovascular mortality in treated hypertensive men with and without diabetes mellitus. Risk Factor Intervention Study Group. *Am J Cardiol.* 1997;80:164-9.
5. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systematic overview of the literature. *Arch Intern Med.* 1997;157:1413-8.
6. Jager A, Kostense PJ, Ruhe HG, *et al.* Microalbuminuria and peripheral arterial disease are independent predictors of cardiovascular and all-cause mortality, especially among hypertensive subjects: five-year follow-up of the Hoorn Study. *Arterioscler Thromb Vasc Biol.* 1999; 19:617-24.
7. Ruilope Luis M and Segura Julian. Predictors of the Evolution of Microalbuminuria. *Hypertension* 2006;48; 832-833.
8. Satchell SC, Tooke JE. What is the mechanism of microalbuminuria in diabetes: a role for the glomerular endothelium? *Diabetologia.* 2008 ;51(5):714-25.
9. Deckert T, Kofoe-Enevoldsen A, Vidal P, *et al.* Size and charge selectivity of glomerular filtration in type 1 (insulin dependent) diabetic patients with and without albuminuria. *Diabetologia.* 1993;36: 244-251.
10. Parving H-H, Mauer M, Fioretto P, Rossing P, Ritz E. Diabetic nephropathy. In: Taal MW, editor. Brenner and rector: the kidney. Philadelphia, PA: Elsevier; 2012. p. 1411–54.
11. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. The Steno hypothesis. *Diabetologia* 1989;32:219–26.
12. Rossing P. Prediction, progression and prevention of diabetic nephropathy. The Minkowski lecture 2005. *Diabetologia* 2006;49(1):11–9.
13. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. *Arch Intern Med* 1997;157:1413–8.
14. Parving H-H. Renoprotection in diabetes: genetic and nongenetic risk factors and treatment. *Diabetologia* 1998;41:745–59.
15. Gaede P, Vedel P, Larsen N, Jensen GV, Parving H-H, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383–93.
16. Astrup AS, Tarnow L, Rossing P, Hansen BV, Hilsted J, Parving H-H. Cardiac autonomic neuropathy predicts cardiovascular morbidity and mortality in type 1 diabetic patients with diabetic nephropathy. *Diabetes Care* 2006;29(2):334–9.
17. Giunti S, Bruno G, Veglio M, Gruden G, Webb DJ, Livingstone S, *et al.* Electrocardiographic left ventricular hypertrophy in type 1 diabetes: prevalence and relation to coronary heart disease and cardiovascular risk factors: the Eurodiab IDDM Complications Study. *Diabetes Care* 2005;28(9):2255–7.
18. Brantsma AH, Bakker SJ, de Zeeuw D, *et al.*; PREVEND Study Group. Extended prognostic value of urinary albumin excretion for cardiovascular events. *J Am Soc Nephrol.* 2008 Sep;19(9):1785-91.
19. Mykkänen L, Zaccaro DJ, Wagenknecht LE, *et al.* Microalbuminuria is associated with insulin resistance in

nondiabetic subjects: the insulin resistance atherosclerosis study. *Diabetes*. 1998; 47(5):793–800.

20. Pontremoli R, Ravera M, Bezante GP, *et al.* Left ventricular geometry and function in patients with essential hypertension and microalbuminuria. *J Hypertens*. 1999; 17(7):993-1000.

21. Wachtell K, Palmieri V, Olsen MH, *et al.* Urine albumin/creatinine ratio and echocardiographic left ventricular structure and function in hypertensive patients with electrocardiographic left ventricular hypertrophy: the LIFE study. Losartan Intervention for Endpoint Reduction. *Am Heart J*. 2002 Feb;143(2):319-26.

22. Dell'omo G, Giorgi D, Di Bello V, *et al.* Blood pressure independent association of microalbuminuria and left ventricular hypertrophy in hypertensive men. *J Intern Med*. 2003;254(1):76-84.

23. Okin PM, Wachtell K, Devereux RB, *et al.*; LIFE Study Investigators. Combination of the electrocardiographic strain pattern and albuminuria for the prediction of new onset heart failure in hypertensive patients: the LIFE study. *Am J Hypertens*. 2008 Mar;21(3):273-9.

24. Cerasola G, Mulè G, Nardi E, *et al.* Usefulness of microalbuminuria in cardiovascular risk stratification of essential hypertensive patients. *Nephron Clin Pract*. 2004; 96(4):c123-30.

25. Gaede P, Vedel P, Parving H-H, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. *Lancet* 1999;353(9153):617–22.

26. Cătălina Arsenescu-Georgescu, Delia Şalaru. Hipertensiunea arterială esenţială. Compendiu de Medicină Internă (editor Cătălina Arsenescu-Georgescu), Editura „Gr. T.Popa" Iaşi, 2014, ISBN 978-606-544-287-0.

27. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013; 34(28):2159-219.