Original Article

Microalbuminuria, an integrated marker of renal and cardiovascular risk in essential hypertension

Fathima Beevi Osman[1*], Bindu Gopinathan Nair[2]

[1,2]Associate Professor, Department of Biochemistry, Government Medical College, Thiruvananthapuram, Kerala, INDIA.
Email: drfathimasalim@gmail.com

Abstract

Introduction: Microalbuminuria reflects the renal expression of a more generalized state of endothelial dysfunction. Microalbuminuria is associated with glomerular hypertension and predicts the onset of frank proteinuria, progressive renal failure and cardiovascular disease which can be attenuated by prompt and scrupulous treatment of hypertension. **Materials and Methods:** Microalbuminuria expressed as albumin creatinine ratio (ACR) was estimated in hypertensive patients (n=31) and healthy normal controls (n=50). Blood pressure (BP) was recorded in all patients and controls. Renal function parameters like urea, creatinine, total protein, albumin and creatinine clearance and lipid parameters like total cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides and high density lipoprotein (HDL) cholesterol estimated in fasting blood samples. Mean and standard deviation(sd) of these values calculated and compared in the two groups using unpaired t test. The correlation of ACR with renal function and lipid parameters were studied by Pearson's correlation coefficient. **Observations and Results:** In hypertensive patients microalbuminuria was significantly higher (43.1±38.2mg/g of creatinine) than in controls (15.08±5.5mg/g of creatinine, p value < 0.001) and showed significant positive correlation with systolic BP ($r = 0.366$; $p < 0.001$), diastolicBP ($r = 0.32$; $p < 0.001$), serum creatinine, blood urea and significant negative correlation with creatinine clearance-indicators of renal dysfunction. Microalbuminuria also showed significant positive correlation with serum total cholesterol, triglycerides and LDL cholesterol which are indicators of cardiovascular disease. **Conclusion:** Microalbuminuria is an effective early marker of renal dysfunction and cardiovascular disease in patients with essential hypertension.

Keywords: Cardiovascular dysfunction, essential hypertension, microalbuminuria, renal dysfunction.

[*]**Address for Correspondence:**
Dr. Fathima Beevi Osman, Associate Professor, Department of Biochemistry, Government Medical College Thiruvananthapuram, Kerala, INDIA.
Email: drfathimasalim@gmail.com

Received Date: 14/11/2016 Revised Date: 09/12/2016 Accepted Date: 04/01/2017

Access this article online	
Quick Response Code:	Website: www.statperson.com
	DOI: 10 January 2017

INTRODUCTION

The worldwide prevalence of lifestyle diseases like hypertension (HTN) and diabetes mellitus have increased dramatically due to industrialization and improved mechanization which has led to decreased work load and consequent development of obesity. Microalbuminuria is associated with glomerular hypertension which predicts the onset of frank proteinuria, progressive renal failure and cardiovascular disease and it can be attenuated by prompt and scrupulous treatment of hypertension. Hypertensive patients with left ventricular hypertrophy (LVH) repeatedly have high glomerular filtration rate (GFR) and filtration fraction than those without ventricular hypertrophy[1]. This suggests that glomerular hyperfiltration in patients with hypertension is related to cardiac remodeling and a generalized vascular adaptation. Monfared *et al* 2013 study showed increased albuminuria is a risk factor for LVH which in turn is an established imdicator of cardiovascular risk[2]. Microalbuminuria reflects the renal expression of a more generalized state of endothelial dysfunction. Recent cross sectional reports in non diabetic populations[3] suggest a more complicated picture. High normal albuminuria rather than microalbuminuria may be representative of initial and early missed stage associated with hyperfiltration, followed by normalization of GFR in the presence of microalbuminuria. Rather than estimating albumin level

How to cite this article: Fathima Beevi Osman, Bindu Gopinathan Nair. Microalbuminuria, an integrated marker of renal and cardiovascular risk in essential hypertension. *International Journal of Recent Trends in Science and Technology.* January 2017; 21(3): 245-250. http://www.statperson.com (accessed 14 January 2017).

in 24 hour urine, a more convenient alternative is to determine the ratio of albumin to creatinine index in early morning urine sample. Creatinine concentration is relatively constant in any subject and index correlates well with the 24 hour total excretion of albumin. Normal ACR is less than30 mg/g of creatinine. Microalbuminuria is said to exist between 30 and 300mg/g of creatinine. Several studies have shown a higher prevalence of microalbuminuria in the presence of impaired glucose tolerance. Since a worse glucose tolerance is part of metabolic syndrome X[4], slight elevation in ACR was also clustered with its typical phenotypes, i.e., hyperinsulinemia, insulin resistance, high triglycerides, low HDL, overweight and BP sensitivity to increased sodium intake. Increased activity of renin angiotensin system is a significant risk factor for the development of target organ damage and cerebral and cardiovascular accidents in hypertensive patients. Further evidence for a role of angiotensin II in development of microalbuminuria is represented by the stronger anti-albuminuric effect and a better renal and cardiovascular outcome exerted by the angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) as compared to other anti-hypertensive drugs. Hence, detection of microalbuminuria at an early stage helps to take proper precaution and to initiate appropriate management in hypertensive subjects.

MATERIALS AND METHODS

This was a case control study carried out in patients with essential hypertension attending the nephrology outpatient clinic of a tertiary care centre in South India (n=31). Patients with frank proteinuria were excluded from the study. Comparative group consisted of age and sex matched healthy normal controls (n=50). BP was measured in all the patients and controls. Height, weight and age of all patients and controls were also noted. Albumin excretion was estimated in the first morning midstream urine sample collected in clean bottles using turbidimetric immunoassay[5-7] done in XL 300 fully automated clinical chemistry analyzer. If the results showed microalbuminuria, urine was retested over the following three months. Urine creatinine was estimated by Jaffe's method and the results were expressed as ACR [8, 9]. If ACR was between 30 and 300mg/g of creatinine on two occasions over a period of three months, a diagnosis of microalbuminuria was made. 6ml of fasting blood samples were also collected from patients and controls under strict aseptic precautions for estimation of glucose, urea, creatinine, total protein, albumin, total cholesterol, HDL cholesterol and triglycerides. From the values of total cholesterol, HDL cholesterol and triglycerides, value of LDL cholesterol was determined using the Friedwald's formula[10]. Creatinine clearance was calculated using Cockroft-Gault formula[11]. Quantitative data were expressed as mean and standard deviation. Statistical analysis was done using SPSS version 22. Comparison of different parameters between the two groups was determined using unpaired t test. The correlation of microalbuminuria with systolic and diastolic BP and renal function parameters like blood urea, serum creatinine and creatinine clearance and lipid parameters like total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides were studied by Pearson's Correlation Coefficient.

OBSERVATIONS AND RESULTS

The study group consisted of 31 patients with essential hypertension and 50 healthy normal controls. The mean systolic BP of patients with essential hypertension was 138.2±9.5mmHg and that of the control group was 115.56±5.3mmHg (Table 1). The observed difference in systolic BP was statistically significant ($p< 0.001$). The mean diastolic BP of patients was 88.1±16.17mmHg and that of the controls was 75±5.8mmHg (Table 1) and the difference was found to be statistically significant ($p< 0.001$). The mean ACR in the hypertension group was 43.1±38.2mg/g of creatinine and that of control group was 15.08±5.5mg/g of creatinine and the observed difference was statistically significant (Table 1, Graph 1)($p< 0.001$).

Table 1: Comparison of study variables in hypertension and control group

Study variables	HTN (N=31)		Control (N=50)		t	*p*
	mean	SD	Mean	SD		
Microalbuminuria (mg/g of creatinine)	43.1	38.2	15.08	5.5	3.9928	<0.001
Blood urea (mg %)	29.27	6.02	21.84	3.73	6.094	<0.001
Serum Creatinine (mg %)	1.06	0.36	0.71	0.35	4.284	<0.001
Urine Creatinine (mg %)	101.47	16.69	123.92	7.41	6.967	<0.001
Creatinine Clearence(ml/mt)	83.83	24.37	121.26	17.58	7.343	<0.001
Serum Protein (g %)	6.71	0.31	6.98	0.2	4.265	<0.001
Serum albumin (g %)	3.75	0.27	3.95	0.15	3.724	<0.001
Fasting blood glucose (mg %)	84.26	8.3	76.52	6.21	4.747	<0.001
Serum total cholesterol (mg %)	225.47	24.98	176.17	25.95	8.261	<0.001

Serum triglyceride (mg %)	122.257	37.44	105.68	51.82	1.527	0.131
HDL (mg %)	42	8.2	49	8.09	3.727	<0.001
LDL (mg %)	153	25.4	106	24.47	8.199	<0.001
Systolic Blood pressure (mmHg)	138.2	9.5	115.56	5.30	11.982	<0.001
Diastolic Blood pressure (mmHg	88.1	16.17	75	5.8	4.275	<0.001

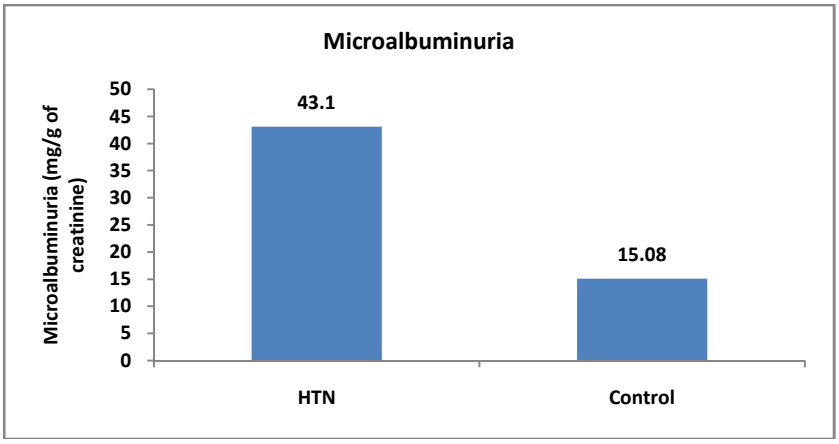

Figure 1: Comparison of microalbuminuria in hypertension and control

Microalbuminuria showed a direct relationship with the duration of hypertension. 57.1% of hypertensive patients with duration of illness less than 3 years were microalbuminuric. This increased to 83.3% in those with hypertension for 3 - 5.9 years, 91.3% in those with hypertension for 6 – 8.9 years and 100% in those who were hypertensive for more than 9 years. The mean blood urea level in hypertension was 29.27±6.02mg% and that of the control group was 21.84±3.73mg% (Table 1, Graph 2) and the difference was statistically significant ($p<$ 0.001).

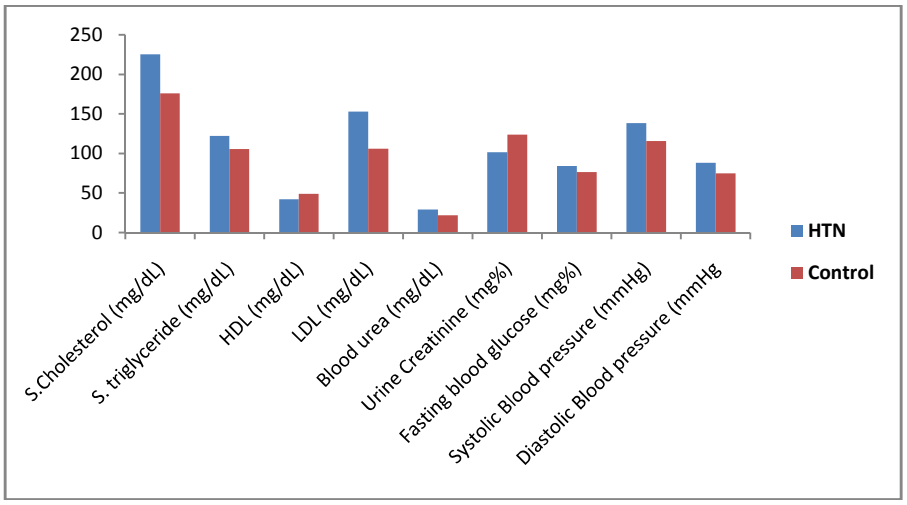

Figure 2: Comparison of study variables in hypertension and control

The mean serum creatinine level in hypertensives was 1.06±0.36 mg% and that of control group was 0.71 ± 0.35 mg% (Table 1, Graph 2) and found to be statistically significant ($p<0.001$). Urine creatinine, creatinine clearance, serum total protein and serum albumin were lower in patients with hypertension than controls (Table 1, Graph 2) and showed statistical significance ($p<0.001$). Serum total cholesterol, LDL cholesterol, triglycerides and fasting blood glucose showed higher values in patients with hypertension when compared to controls (Table 1) and differences were statistically significant ($p<0.001$). However serum triglycerides did not show any statistically significant difference ($p=0.131$) (Table 1, Graph 2).

Table 2: Correlation of study variables with ACR in hypertension

Correlation between ACR and other parameters	Pearson correlation	
	r	*p*
FBS	0.65	<0.001
DBP	0.32	<0.001
SBP	0.366	<0.001
Blood Urea	0.748	<0.001
Serum Creatinine	0.783	<0.001
Urine Creatinine	-0.681	<0.001
Creatinine Clearence	-0.667	<0.001
Total Protein	-0.652	<0.001
Serum albumin	-0.737	<0.001
Total cholesterol	0.488	<0.001
Triglyceride	0.278	0.001
LDL cholesterol	0.469	<0.001

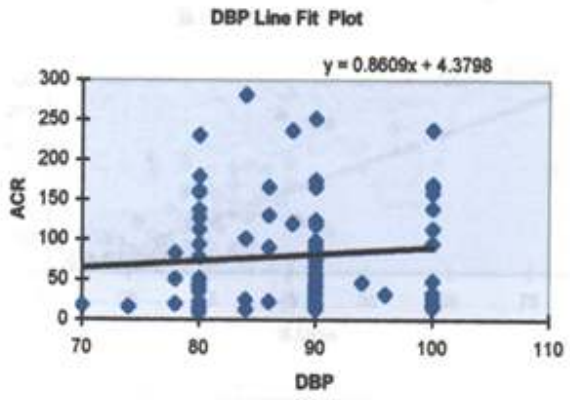

Figure 1

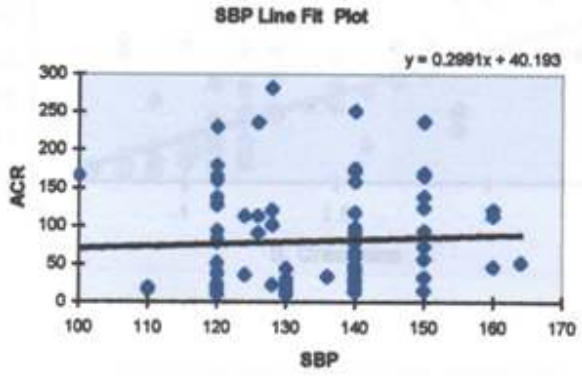

Figure 2

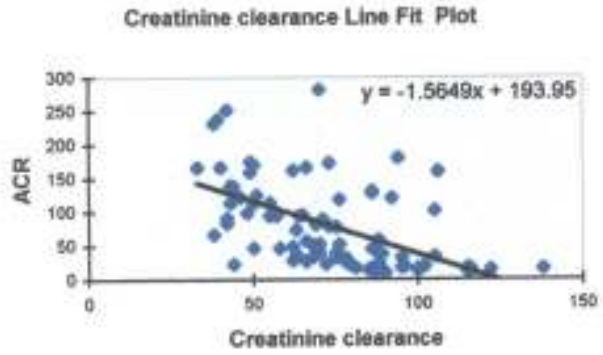

Figure 3

Legend: Figure 1: Correlation of ACR with diastolic BP (DBP); **Figure 2:** Correlation of ACR with systolic BP (SBP); **Figure 3:** Correlation of ACR with creatinine clearance

Correlation between ACR and other study parameters was done using Pearson's correlation. ACR showed significant positive correlation with both systolic (Table 2, Figure 2) (r=0.366) (p<0.001) and diastolic BP (Table 2, Figure 1) (r=0.32) (p<0.001), the renal function parameters like blood urea (r=0.748) (p<0.001) and serum creatinine (r=0.783)(p<0.001) and significant negative correlation with urine creatinine (r=-0.681) (p<0.001), creatinine clearance (Table 2, Figure 3) (r=-0.667) (p<0.001), serum total protein(r=-0.652) (p<0.001) and serum albumin(r=-0.737) (p<0.001). ACR also showed significant positive correlation with cardiovascular markers like serum total cholesterol, LDL cholesterol and triglycerides (Table 2, Graph 2) (p<0.001).

DISCUSSION

The present study has demonstrated that the albumin creatinine ratio is significantly high in hypertensives (43.1±38.2mg/g of creatinine) compared to controls (15.08±5.5 mg/g of creatinine).Previous studies also showed correlation between microalbuminuria and blunted or absent nocturnal dipping of BP in hypertensive patients with microalbuminuria compared to those with normal albumin excretion rates and normotensive healthy individuals[12].The prevalence of microalbuminuria was increased with increased duration of hypertension. Inthe study group patients were on different antihypertensive treatment including ACEinhibitors, calcium channel blockers and diuretics, but the effects of these drug groups on microalbuminuria were not studied. In hypertensive patients with type 2 diabetes mellitus,an elevated urinary albumin excretion was associated with a higher left ventricular mass index, an increased prevalence of concentric left ventricular hypertrophy and also a markedly impaired diastolic function[12]. In our study also microalbuminuria was positively correlated with both systolic and diastolic BP in hypertensive patients (Table 2) (Figure 1and 2). Mean values ± SD of systolic BP in the study group was 138.2±9.5 mmHg and that of the control group was 115.56±5.3 mm Hg (Table 1, Graph 2)(p<0,001)[13,14]. In the Appropriateness of Blood pressure Control in Diabetes (ABCD) study in patients with type 2 diabetes mellitus, intensive treatment versus conventional decreased the progression from normoalbuminuria to microalbuminuria[15]. Mean diastolic BP± SD in the study group was 88.1± 16.77 mmHg and that of control group was 75±6.8 mmHg (Table 1,Graph 2) (p<0.001). Microalbuminuria was positively correlated with diastolic BP in hypertensive patients[16,17]. Studies by Tsioufis C *et al* have shown that microalbuminuria was closely related to impaired arterial elasticity in untreated patients with hypertension[18]. Another study by Pedrinelli*et al* in essential hypertension showed a significant association of hypertension and microalbuminuria[19]. A study by Mogensen CE *et al* showed that blood pressure should be as low as possible especially in diabetes to prevent diabetic complications. Renal function parameters like blood urea and serum creatinine values were higher in hypertensive patients compared to controls (Table 1,Graph 2) (p<0.001). Similarly urine creatinine,serum total proteins, serum albumin and creatinine clearance levels were significantly decreased in the study group when compared to control group(Table 1, Graph 2) (p<0.001)[20,21]. No change in creatinine clearance was observed in ABCD trial[15] and microalbuminuria reduction with valsartan study[22] with much shorter follow up. The renal function parameters like blood urea and serum creatinine also showed significant positive correlation with ACR in hypertensive patients (Table 2) (p<0.001) and significant negative correlation was found between ACR and renal function parameters like urine creatinine, creatinine clearance, serum proteins and serum albumin (Table 2, Figure 3) (p<0.001). Hypertensive microalbuminuria is characterized by unchanged GFR,decreased renal plasma flow, increased filtration fraction, elevated vascular resistance[23-26] and exhaustion of renal functional reserve[27]. The mean lipid parameters like total cholesterol and LDL cholesterol showed significantly higher values in patients with hypertension compared to controls (Table 1, Graph 2) (p<0.001). The mean HDL cholesterol levels showed lower values in hypertensive patients than controls (Table 1, Graph 2)(p<0.001). However serum triglycerides did not show any statistically significant difference between the study group and control group (Table 1,Graph 2) (p=0.131). Serum total cholesterol, LDL cholesterol and triglycerides showed significant positive correlation with ACR in the study group (Table 2) (p<0.001).Since systolic and pulse pressure predict cardiovascular disease in hypertension[28] and both reflect decreased arterial compliance and a more advanced atherosclerotic process[29], this imply a direct link between microalbuminuria and macro and microvascular disease[30]. Prospective data from 5545 nondiabetic subjects of the HOPE cohort confirmed the existence of a continuous relationship between albuminuria and cardiovascular events (a composite end point including myocardial infarction,cerebrovascular accidents or cardiovascular death[31]. In addition the consistent body of knowledge showing independent link between albuminuria and cardiovascular morbidity and mortality[31-33] should prompt more widespread screenings in essential hypertensive patients, similar to the approach proposed for other risk markers in hypertension such as left ventricular mass[34]. Thus microalbuminuria, an integrated marker of cardiovascular risk, may be particularly effective to identify patients at higher absolute risk in whom prompt preventive treatment will be more beneficial than patients with lower absolute risk.

CONCLUSIONS

The present study has demonstrated higher levels of microalbuminuria in patients with essential hypertension which showed significant positive correlation with both systolic and diastolic hypertension and the renal function parameters like blood urea and serum creatinine. ACR also showed significant negative correlation with urine creatinine and creatinine clearance establishing it as a reliable indicator for detection of early renal dysfunction in the risk population so that prompt management can be initiated to effectively reduce the morbidity and mortality.

Microalbuminuria is significantly correlated with dyslipidemia characterized by elevated levels of total cholesterol, LDL cholesterol and triglycerides in the study group which reflect atherosclerotic process thus contributing to increased cardiovascular risk.

REFERENCES

1. Schmieder RE, Messerli FH, Garavaglia G et al. Glomerular hyperfiltration indicates early target organ damage in essential hypertension. JAMA. 1990: 264:2775.
2. Monfared A, Salari A et al. Left ventricular hypertrophy and microalbuminuria in patients with essential hypertension. Iran J Kidney Dis. 2013 ; 7:192-7.
3. Pinto-SSJ et al. Urinary albumin excretion is associated with renal functional abnormalities in a non-diabetic population. J Am Soc Nephrol. 2000; 11:1882-1888.
4. Reaven GM. Insulin resistance and human disease: a short history. J Basic Clin Physiol Pharmacol. 1998;9:387-406.
5. Landgraf L,Modi E, Horn K, et al.Immunoturbidimetric Assay for the Determination of Microalbuminuria Using the Hitachi Analyzer.J Clin Chem Clin Biochem. 1987; 25:683-687.
6. Schmidz et al. Diabetic Medicine 1988;5:126.
7. Urine albumin excretion; NKDEP Guidelines for Classification of Chronic Kidney Disease.
8. Mangili R et al. and the Italian Microalbuminuria Study Group. Prevalence of hypertension and microalbuminuria in adult type 1 (insulin dependent) diabetic patients without renal failure in Italy: validation of screening techniques to detect albuminuria. Acta Diabetol. 1992;29: 156-166.
9. Jensen JS et al. Detecting microalbuminuria by urinary albumin/creatinine concentration ratio. Nephrol Dial Transplant. 1997; 12:6-9.
10. Friedwald WT, Levy RI, Frederickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultra centrifuge. Clin. Chem. 1972; 18:499-502.
11. Cockroft DW, Gault MH: prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16:31-41.
12. Picca M, Agozzino F, Pelosi G. Infuence of microalbuminuria on left ventricular geometry and function in hypertensive patients with type 2 diabetes mellitus. Ital Heart. J. 2003; 4:48-52.
13. Tagle R, Acevedo M, Vidt DG. Microalbuminuria: Is it a valid predictor of cardiovascular risk? Cleve Clin J Med. 2003; 70:255-261.
14. Hughes S. Novel cardiovascular risk factors. J Cardiovasc Nurs. 2003;18:131-138.
15. Schrier RW, Estacio RO, Ester A et al. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney. Int. 2002;61:1086-1097.
16. Semplicini A et al. The Li^+/Na^+ exchange in hypertension, Front Biosci. 2003;01:912-29.
17. Benz WJ, Ashraf M et al. Effects of resistance versus aerobic training on coronary artery disease risk factors. Exp Biol Med (Maywood). 2003;228:434-40.
18. Tsioufis C et al. University of Athens, Greece. Microalbuminuria is closely related to impaired arterial elasticityin untreated patients with essential hypertension. Nephron Clin Pract. 2003;93: 106-11.
19. Pedrinelli R et al. Microalbuminuria a parameter independent of metabolic influences in hypertensive men. J Hypertens. 2003; 21:1163-9.
20. Lane JT. Microalbuminuria as a marker of cardiovascular and renal risk in type 2 diabetes mellitus: a temporal perspective. Am J Physiol Renal Physiol.2004;286:442-50.
21. Rippin JD et al. Cost effective strategies in the prevention of diabetic nephropathy. Pharmaco economics. 2004; 22:9-28.
22. Viberti GC, Wheeldon NM. Microalbuminuria reduction with Valsartan in patients with type 2 diabetes mellitus. Circulation. 2002;106:672-8.
23. Mimran A, Ribstein J, DuCailar G. Is microalbuminuria a marker of early intrarenal vascular dysfunction in essential hypertension? Hypertension. 1994;23:1018-1021.
24. Reid M, Bennett F, Wilkes R, Forrester T. Microalbuminuria, renal function and waste hip ratio in black hypertensive Jamaicans. J Hum Hypertens. 1998;12:221-227.
25. Mattei P et al. Microalbuminuria and renal hemodynamics in essential hypertension. Eur J Clin Invest. 1997;27:755-760.
26. Pontrimoli R et al. Increased renal resistive index in patients with essential hypertension: a marker of target organ damage. Nephrol Dial Transplant. 1999;14:360-365.
27. Losito A, Fortunati F, Zampi I, Del Favero A. Impaired renal functional reserve and albuminuria in essential hypertension. Br Med J. 1988;296:1562-1564.
28. Verdecchia P. Prognostic value of ambulatory blood pressure:current evidence and clinical implications. Hypertension. 2000;35:844-851.
29. Smulyan H, Safar ME. Systolic blood pressure revisited. J Am Coll Cardiol. 1997;29:1407-1413.
30. Jensen JS. Microalbuminuria andthe risk of atherosclerosis. Clinical epidemiological and physiological investigations. Med Bull. 200;47:63-78.
31. Gerstin HC et al. Albuminuria and risk of cardiovascular events, death and heart failure in diabetic and non diabetic individuals. JAMA. 2001;421-426.
32. Pedrinelli R, Dell' Omo G, Penno G, Mariani M. Nondiabetic microalbuminuria, endothelial dysfunction and cardiovascular disease. Vasc Med.2001;6:257-64.
33. Roest M et al. Excessive urinary albumin levels are associated with future cardiovascular mortality in post menopausal women. Circulation. 2001;103:3057-3061.
34. Agabiti-Rosei E et al. Arterial hypertension and heart diseases. Diagnostic-therapeutic guidelines. JointCommission of the National Association of Hospital Cardiologists. The Italian Society of Cardiology and the Italian Society of Arterial Hypertension. Cardiologia. 1999; 44:299-312.

Source of Support: None Declared
Conflict of Interest: None Declared