Microalbuminuria In Essential Hypertension

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Abstracts: **Background & objectives:** Microalbuminuria has been described as an early sign of vascular damage in certain high risk goups such as diabetes, hypertension & family history of cardiovascular renal disease. In diabetes mellitus the prognostic value of microalbuminuria as a marker of early nephropathy and increased cardiovascular risk has been well established. The aim of this study is to establish the prevalence of microalbuminuria in nondiabetic essential hypertensive patients and its relation with target organ damage. **Material and Methods**: 100 non diabetic essential hypertensive patients attending OPD as well as admitted in the tertiary care hospital of Jamnagar were included in this study. They underwent detailed clinical examination. A single early morning urine sample was used to measure microalbuminuria by Micral test strip and urine creatinine was measured to establish albumin creatinine ratio. **Results:** The age of patients selected for study varied from 35 to 76 years; mean age being 51.5 years. 52% were males and mean duration of hypertension was 3.9 +/- 3.9 yrs. Microalbuminuria was found in 46% of the patients and showed significant association with male gender ($p=0.001$), age ($p<0.05$) & target organ damage in any form ($p<0.05$). **Interpretation and conclusion:** Measuring urinary albumin excretion (UAE), a simple, low cost and readily available test, can be regarded as a cost effective way to identify nondiabetic essential hypertensives at high risk and can thus help to prevent the development of complications by aggressive treatment to get down to target blood pressure.[Dayal A NJIRM 2014; 5(1) : 76-81]

Key Words: Blood Pressure, Hypertension, Microalbuminuria(MAU), Target Organ Damage (TOD).

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Introduction: Hypertension affects, approximately 1 billion worldwide[1]. The relationship between blood pressure and risk of coronary vascular disease is continuous, consistent and independent of other risk factors[1]. Microalbuminuria (MAU) has been associated with a number of unfavourable biohumoral risk factor as well as with subclinical organ damage in non diabetic patients with primary hypertension[2]. Microalbuminuria reported in 10-40% of non- diabetics with hypertension, may serve as an early indicator of risk to develop subsequent proteinuria and progressive renal impairment[3].Until late in the course of hypertensive nephropathy, renal damage is asymptomatic and laboratory findings are subtle. The first objective sign of renal involvement is a small increase in the amount of albumin in urine. The normal range for urinary albumin to creatinine ratio is less than 30mg/gm; albumin to creatinine ratio in the range of 30-300mg/gm, which can be missed with routine clinical laboratory methods (e.g. Dipstick) is referred to as "Microalbuminuria"[3]. The recent Joint National Commission on Hypertension (JNC VII) report includes microalbuminuria as evidence for the presence of target organ damage. Target Organ Damage indicates the need for more aggressive control of blood pressure[4]. However, routine evaluation of Microalbuminuria is not recommended by international guidelines as part of the diagnostic workup of every hypertensive patient[2]. The purpose of this study is to evaluate the prevalence of microalbuminuria in patients admitted or attending outpatient clinic in a tertiary care hospital of Jamnagar, Gujarat with essential hypertension and target organ damage.

Material and Methods : This study was carried out on 100 primary hypertensive, non-diabetic patients attending outpatient clinic as well as admitted in tertiary care hospital of Jamnagar from January 2003 to December 2005 with prior approval of the Institutional Ethics Committee . After informed consent had been obtained, each individual's name, age, sex, occupation, duration of disease were recorded and history of symptoms and complications if any taken. Patients were then subjected to (a) clinical blood pressure measurement. (b) Blood and urine sampling g for routine biochemistry – blood sugar, creatinine and urine routine-microscopy. (c) Urine tested for microalbuminuria. (d) Patients were further

subjected to electrocardiography to evaluate left ventricular hypertrophy(LVH) and coronary artery disease. (e) Fundoscopy was performed to record changes of hypertensive retinopathy.

Patients with presence of urine sugar, co-existence of diabetes mellitus, neoplastic disease, urinary tract infections and renal stones were excluded from the study. Blood pressure was measured by a physician with the patient in sitting position, after proper rest with a mercury sphygmomanometer with adult cuff size. Two consecutive readings were taken. The presence of microalbuminuria was evaluated in each patient by micral test, manufactured by Roche Diagnostics GmbH Mannheim Germany, based on immunoprecipitation technique. Early morning urine samples were collected. The test strip has been evaluated by several authors[5,6,7] and has a 80-90% sensitivity and specificity. These results coupled with the ease and convenience of both specimen collection and the micral test itself support the use of test as a valuable screening tool for microalbuminuria in patients with hypertension. Due to the variation in urinary flow rate and concentration, the excreted urinary albumin was adjusted to creatininuria and albumin to creatinine ratio was established. Urine creatinine was estimated by modified Jaffe's reaction. Urinary albumin creatinine ratio(ACR) of 30-300 mg albumin/g creatinine was considered positive for microalbuminuria and value less than 30 mg albumin/g creatinine was considered negative.

Results: Demographic characteristics of the study patients are reported in table 1. The age of patients selected for study varied from 35 to 76 years, mean age being 51.5 +/- 12.5 years. Out of 100 patients 52% were males and 48% were females. Most of the hypertensives (57%) had hypertension ranging from 0-3 yrs. The overall frequency of microalbuminuria, LVH and hypertensive retinopathy in the study subjects was 46%, 39% and 40% respectively.

Table 2 shows the univariate analysis of the determinants of microalbuminuria in study subjects. Microalbuminuria was found to be significantly associated with age ($p< 0.05$) and gender with 61.53% of males as compared to 29.2% of females testing positive ($p= 0.001$). 80% of the patients having hypertension for more than 7.5 years were microalbuminuric though statistical significance could not be established.

Table I: Demographic Profile of Study Subjects

Demographic Variable	Frequency	Percentage
1.Age Group (in yrs)		
31-40	13	13 %
41-50	39	39 %
51-60	26	26 %
61-70	14	14 %
71-80	8	8 %
2.Gender		
MALES	52	52 %
FEMALES	48	48 %
3.Duration of Hypertension(in yrs)		
0-1.5	40	40 %
1.5-3	17	17 %
3-4.5	10	10 %
4.5-6	5	5 %
6-7.5	13	13 %
7.5-9	6	6 %
>9	9	9 %
4. Microalbuminuria Present	46	46%
5.Left Ventricular Hypertrophy(LVH)	39	39%
6. Retinopathy	40	40%
7. Target Organ Damage(TOD)	56	5%

The mean systolic B.P. of microalbuminuric group was higher (174.6 +/- 23.8mm of Hg) than the normoalbuminuric group (150.5 +/- 21.1 mm of Hg), whereas the mean diastolic B.P. was almost similar 100.4+/- 9.2 mm of Hg in the microalbuminuric group vs. 96.4 +/- 9.7 mm of Hg in the normoalbuminuric group.

Table 3 shows the correlation between microalbuminuria and target organ damage. Target organ damage in any form(Retinopathy, LVH, coronary artery disease) was found to be significantly associated with microalbuminuria)($p<0.05$).

Table2:Univariate Analysis of Determinants of Microalbuminuria in Patients of Essential Hypertension

Variable	Micro-albumin-uria Present	Micro-albumin-uria Absent	Total	P value
1.Age Group(in yrs)				
31-40	3	10	13	0.6776
41-50	11	28	39	0.5116
51-60	15	11	26	0.0428
61-70	11	3	14	0.0056
71-80	6	2	8	0.0294
2.Gender				
MALES	32	20	52	0.0012
FEMALES	14	34	48	1
3.Duration of Hypertension(in yrs)				
0-1.5	18	19	37	0.0768
1.5-3	3	15	18	0.001
3-4.5	2	8	10	0.0073
4.5-6	2	4	6	0.0619
6-7.5	8	5	13	0.3401
7.5-9	5	1	6	0.8686
>9	8	2	10	1
4.Systolic B.P(in mm of hg)				
101-120	0	1	1	0.3061
121-140	3	4	7	0.6625
141-160	12	27	39	0.1726
161-180	20	12	32	0.4646
>180	11	10	21	1
5.Diastolic B.P(in mm of Hg)				
0-80	1	3	4	0.4076
81-90	5	8	13	0.6038
91-100	28	31	59	0.8925
101-110	8	8	16	1
111-120	4	4	8	1

Table 3: Correlation between Microalbuminuria and Target Organ Damage (TOD)

Microalbuminuria	TOD Present	TOD Absent	Total
Present	32	14	46
Absent	24	30	54
Total	56	44	100

Chi-Square=5.383, P=0.0203 (p<0.05, significant)

Discussion : The invention of sensitive immunoassays in the beginning of 1960's allowed the measurement of previously undetectable amount of albumin in urine[8,9].Increased urinary albumin excretion has been shown to be an independent predictor of cardiovascular morbidity and mortality in patients with essential hypertension[10]. Prevalence of MAU varied from about 4% to 46% across different studies and these differences may be explained by the huge intra-individual variability in UAE, discrepancies in the techniques of measurement and different definitions of MAU[11]. Prevalence in present study is 46% which is on a higher side; this may be because in a tertiary hospital the patients presenting with hypertension are usually having uncontrolled B.P. as is seen in the higher number of study subjects having systolic B.P. more than 160mm of Hg. Also age and race seem to exert a significant influence on UAE and may account for some of the variability reported in literature[12]. The type of urine sample collected for evaluation that is random, 24 hours, overnight collection has also been shown to be responsible for the variability amongst the various studies. The measurement of the albumin creatinine ratio on first voided morning samples used in the present study was shown to be an accurate and reproducible predictor of the AER, perhaps because of the relative stability of renal hemodynamic during night rest[12].

Microalbuminuria was found to be significantly associated with male gender and elderly age group ($p<0.05$) (table 1). That microalbuminuric patients were more likely to be males was also shown in studies done by Pontremoli R et al[12], Badiger S et al[13] and Bacanu EV et al[14]. Increasing prevalence of microalbuminuria with increasing age was also reported by Agrawal B et al[15] and Hitha B et al[16].

In present study 80% of the patients having hypertension for more than 7.5 years had microalbuminuria demonstrating increased frequency with increasing duration of hypertension. However, statistical significance was not seen in patients with duration of more than 5 years. As the patients with longer duration must have received anti-hypertensives during the course of the disease, this may account for the loss of association seen with increasing duration. Antihypertensive therapy of any kind is able to

lower UAE in essential hypertensives by simply lowering blood pressure[17]. Though effect of drugs/treatment was not evaluated in this study, other studies have shown that even in treated patients prevalence can be as high as 25% when diuretics and beta blockers are used[18,19]. ACE inhibitors have been shown to exhibit a higher capacity to decrease microalbuminuria in hypertensive patients that goes beyond their capacity to decrease renal perfusion pressure[20].

In this study, mean systolic B.P. of hypertensive patients with microalbuminuria was higher (174.6mm of Hg) than the normoalbuminuric group, but the mean diastolic blood pressure was almost similar in the two groups. This signifies a higher pulse pressure in the microalbuminuric group though not statistically significant. The principal components of blood pressure consists of both a steady component (mean arterial pressure MAP) and a pulsatile component (pulse pressure, PP). PP, the difference between SBP & DBP is also made up of two major components – one due to ventricular ejection interacting with the viscoelastic properties of large arteries and the other due to wave reflection (indirect)[21]. Pulse pressure reflects the degree of stiffness of the arterial tree, regardless of whether they are caused by increased systolic (SBP) and / or reduced diastolic pressure (DBP)[22]. These findings further emphasize the role of the kidney as a sensor of cardiovascular risk and are in agreement with previous studies which show that even subclinical abnormalities such as presence of microalbuminuria are powerful predictors of cardiovascular damage. Systemic pulse pressure could be a marker of early intrarenal vascular stiffness and might play a role in the development of renal damage[22] and the increased urinary albumin excretion. In clinically defined hypertension and in persons at risk of hypertension, renal hemodynamics are characterized by a post glomerular vasoconstriction, which maintains glomerular filtration in the normal range despite a low renal blood flow[23].Thus the influence of high systemic pressure on the glomerulus could favour the onset of microalbuminuria however the exact pathogenetic mechanism and effect of other possible mechanisms could not be investigated by the present study.

Significant association was found between microalbuminuria and target organ damage (left ventricular hypertrophy, coronary artery disease, hypertensive retinopathy) in the present study. Major ECG abnormalities and vascular retinal changes are thought to reflect pressure overload and atherosclerotic vascular damage in patients with essential hypertension and thereby are considered predictors of future vascular events[12].Similar findings were also shown by study done by Agrawal B et al[15] and Leoncini G et al[2], Hitha B et al[16], Badiger S et al[13].

Jager et al[24] observed that microalbuminuria and peripheral arterial disease were both independent predictors of cardiovascular and all cause mortality, especially among hypertensive individual. In a prospective study of 2085 non diabetic individuals the relative risk of ischemic heart disease associated with microalbuminuria was 2.3 and was independent of other conventional atherosclerotic risk factors[25]. Hypertension is associated with functional and morphological alterations of the endothelium, which disturbs delicate balance of endothelium-derived factors resulting in endothelial dysfunction as reported by Sainani GS et al[26] study group. The endothelial dysfunction could then facilitate the maintenance of elevated peripheral resistance, which would favour the occurrence of atherosclerosis. The clinical markers of the generalized endothelial dysfunction becomes manifest in several forms. Microalbuminuria is one such marker, which marks the onset of endothelial dysfunction related to the kidney and whole vascular system[13].Thus microalbuminuria can be considered as a specific integrated marker of cardiovascular risk and target organ damage in essential hypertension. So it is very important to screen for microalbuminuria in early stages of essential hypertension, which if treated early can prevent atherosclerotic processes in the entire vascular system[13].

Conclusion : Microalbuminuria is consistently associated with patients having essential hypertension and seems to be a simple and accurate method to detect patients at high risk for cardiovascular & probable renal damage.

Refrences :

1. The seventh report of the Joint National committee on prevention, detection, evaluation and treatment of high blood pressure (JNC 7 – 2003).
2. Leoncini G, Sacchi G, Ravera M et al. Microalbuminuria is an integrated marker of subclinical organ damage in primary hypertension. J. of Human Hypertension 2002; 16: 399-404.
3. Hoegholm A, Bang LE, Kristensen KS, Neilsen JW, Holm J. Microalbuminuria in 411 untreated individuals with established hypertension, white coat hypertension, and normotension. Hypertension Jul 1994; 24(1): 101-5.
4. Freedman BI, Beck SR, Rich SS. Meiss G, Lewis CE. A Genome wide scan for urinary albumin excretion in hypertensive families. Hypertension 2003; 42: 291-296.
5. Bangstad HJ, Kenneth T, Jorgensen KD, Hanssen KF. New semiquantitative dipstick test for microalbuminuria. Diabetes Care 1991; 14: 1094–1097
6. Poulsen PL, Hansen B, Amby T, Terkelsen T, Mogensen CE. Evaluation of a dipstick test for microalbuminuria in three different clinical settings, including the correlation with urinary albumin excretion rate. Diabete Metab 1992; 18: 395–400
7. Minetti EE, Cozzi MG, Granata S and Guidi E. Accuracy of the urinary albumin titrator stick 'Micral-Test'in kidney-disease patients. Nephrol Dial Transplant 1997; 12: 78–80
8. Mogensen CE : Microalbuminuria, blood pressure and diabetic renal disease: origin and development of ideas in : the kidney and hypertension in diabetes Mellitus : Edited by Mogensen Boston. Kluwer academic Publishers 2000: 655-706.
9. Thomas SM, Viberti GC. Is it possible to predict diabetic kidney disease (Review). J Endocrinol 2000; 23: 44-53.
10. Bigazzi R, Bianchi S, Campese VM, Baldari G. Prevalence of microalbuminuria in a large population of patients with mild to moderate essential hypertension. Nephron 1992; 61: 94-97.
11. Verdecchia P and Reboldi GP. Hypertension and microalbuminuria: the new detrimental duo. Blood Pressure 2004; 4(13): 198-211.
12. Pontremoli R, Sofia A, Ravera M, et al. Prevalence and clinical correlates of microalbuminuria in essential hypertension: The MAGIC study. A Genoa investigation on complications. Hypertension 1997; 30(5): 1135-1145.
13. Badiger S, Sandeep HM, Talikoti SC, Biradar MS. A study of microalbuminuria and target organ damage in patients with essential hypertension. Int J Biol Med Res. 2012; 3(1):1351-1355
14. Bacanu EV, Bacanu ME, Botez C. Microalbuminuria in essential hypertension at patients with or without type 2 diabetes.Proc. Rom. Acad., Series B 2011; 2: 145-154.
15. Agrawal B, Berger A, Wolf K, Luft FC. Microalbuminuria screening by reagent strip predicts cardiovascular risk in hypertension.J Hypertens Feb1996; 14 (2): 223-8.
16. Hitha B, Pappachan JM, Pillai HB, Sujathan P, Ramakrishna CD, Jayaprakash K et al. Microalbuminuria in patients with essential hypertension and its relationship to target organ damage: An Indian Experience. Saudi J Kidney Dis Trannspl 2008; 19 (3): 411-419.
17. Rodicio JL, Campo C, Ruilope LM : Microalbuminuria in essential hypertension. Kidney International 1998; 54(Suppl.68): 51-54.
18. Ruilope LM, Alcazar JM, Rodicio JL : Renal consequences of arterial hypertension. J Hypertens 1992; 10(suppl.7): 85-90.
19. Cottone S, Cerasola G. Microalbuminuria fractional clearance and early renal permselectivity changes in essential hypertension. Am J Nephrol 1992; 12: 326-329.
20. Ruilope LM, Alcazar JM, Hernandez E, Praga M, Lahera V, Rodicio JL. Long term influences of antihypertensive therapy on microalbuminuria in essential hypertension. Kidney Int 1994; 45 (suppl.45): 171-173.
21. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in

predicting risk for coronary heart disease ? The Framingham Heart Study. Circulation 1999; 100: 354-360.
22. Viazzi F, Leoncini G, Parodi D et al. Pulse pressure and subclinical cardiovascular damage in primary hypertension. Nephrol Dial Transplant 2002; 17: 1779-1785.
23. Crillo M, Stellato D, Laurenzi M, Panarelli W, Zancheti A, and Santo NG. The Gubbio study collaborative research group. Pulse pressure and isolated systolic hypertension. Association with Microalbuminuria. Kidney International 2000; 58: 1211-1218.
24. 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: 617-624.
25. Borch-Johnsen K, Feldt-Rasmussen B, Strandgaard S, Scroll M, Jensen JS. Urinary albumin excretion : an independent predictor of ischaemic heart disease. Arterioscler Thromb. Vasc Biol 1999; 19: 1992-1997.
26. Sainani GS, Maru GV. Role of endothelial cell dysfunction in essential hypertension. JAPI.2004; 52: 966- 969

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