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Prospective Observational Study of the Prevalence and Profile of Patients with Microalbuminuria in India

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Abstract

Background: Microalbuminuria (MA), a marker of diffuse endothelial dysfunction has been associated with adverse health outcome in diabetics, hypertensives, and metabolic syndrome and is predictor of all-cause mortality in the general population. There is lack of epidemiological data, regarding prevalence of MA in Indian population, diabetic, hypertensive or otherwise. **Objectives**: Our objective was to analyze the prevalence and profile of MA in a cross section of Indian population, to evaluate the relationship between MA and chronic diseases and to establish the importance of including urine Albumin Creatinine Ratio (ACR) estimation in routine health checkup clinic. **Methods**: A cross sectional observational study was undertaken at the health checkup clinic of a tertiary care hospital between September 2016 and February 2018. Data of randomly selected group of patients (n=360) were obtained. Demographic data and medical history were collected by interview. Urine ACR was done from routine biochemistry. Selected patients were screened for presence of urine MA and compared with those who did not have MA. **Results**: 6.3% patients had MA with no obvious risk factors. Prevalence of MA was 15% in females, 14% in males, 9.2% in smokers, 28% among diabetics, 22% among hypertensives, 25% among patients with ischemic heart disease, 15% among patients with dyslipidemia, 24% among patients with hyperuricemia, and 24% among patients with metabolic syndrome. **Conclusion:** Patient without any identifiable risk factor may have MA. Therefore urine ACR should be included in routine health checkup clinic.

Keywords: microalbuminuria, clinical profile, India

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Introduction

Microalbuminuria (MA) refers to the appearance of small but abnormal amounts of albumin in the urine which cannot be detected using the conventional dipstick method. It can also be said as the excretion of protein greater than 30 mg and lesser than 300 mg of albumin per day in urine.

In normal humans albumin is not excreted via glomerulus. But there is a small amount of protein (below 30mg), which is secreted from tubules and excreted regularly along with the urine. In some cases such as diabetic nephropathy, glomerulonephritis or amyloidosis, more amount of proteins can cross the glomerulus and are found in urine.

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Clinically microalbuminuria becomes an important finding, as it is not just a manifestation of glomerulopathy but also a marker of endothelial dysfunction and is an independent risk factor for cardiovascular disease (1).

Recent studies have shown that microalbuminuria can be controlled by putting them under Angiotensin converting enzyme (ACE) inhibitors or angiotensin-II type 1 receptor antagonists. These antihypertensive agents target the renin-angiotensin system and help to slow the progression of the renal disease and provide cardio protection in patients with type 2 diabetes mellitus (T2 DM) and microalbuminuria.

It is a marker of endothelial dysfunction and increased risk for cardiovascular morbidity and mortality, especially but not exclusively, in high risk population such as diabetes and hypertensive (2).

In the past decades, a number of studies have demonstrated that MA is not only a risk factor for Diabetic nephropathy, but also an independent risk factor for cardiovascular mortality in T1 DM , T2 DM and apparently healthy controls(3,4).

In healthy controls, about 5% albumin/ hr leave the vascular bed and returns through lymphatic vessels in the following hrs. Therefore an increase in albumin in urine is indicative of universal vascular leakage, which should be present in patients as well as healthy controls with MA. In this stage of MA, excess loss of albumin in urine may not reflect kidney disease but rather a universal capillary leakage, which could be portend to cardiovascular disease (CVD)(5).

Endothelium plays a very central role in vascular function. A number of markers in plasma reflects endothelial cell function, including von willebrand factor (vWF), angiotensin converting enzyme (ACE), adhesion molecule S VCAM1, S ICAM1 and e selectin (6,7). It has been shown that vWF concentration was higher in hypertension (HTN) with MA than HTN without MA and controls. MA in essential HTN may reflect systemic dysfunction of vascular endothelium (8,9). In another study it was seen that development of MA is strongly related with endothelial dysfunction (rise in vWF) leading to new CV events in T2DM.

In other words, it is suggested that endothelial dysfunction is the initial event in development of MA (10)

There is increased incidence of metabolic syndrome in Indians, worldwide. Endothelial dysfunction plays an important role in it by causing increased Mononuclear cell adhesion, increased concentration of cellular adhesion molecules, increase of asymmetric dimethyl arginine, and decreased endothelial-dependent vasodilatation (11).

The alarming increases in central obesity in metabolic syndrome seem to be behind the twin epidemic of T2 DM and CVD in the Indian subcontinent (12). Sedentary life-style and easy-availability of energy-dense food are the driving force for this growing menace. By doing MA in metabolic syndrome we can detect endothelial dysfunction in metabolic syndrome, can start early intervention to reduce morbidity and mortality.

It has been shown that MA is a predictor of all cause mortality in the general population (13). There is lack of epidemiological data, however, regarding the prevalence of MA in the Indian population, diabetic, hypertensive or otherwise. So our intension was to study the prevalence and profile of MA in a cross section of Indian population to detect the prevalence of the ailment in our community.

Aims and Objectives:

To analyze the prevalence and profile of microalbuminuria in a cross section of Indian population,

To evaluate the relation between albumin excretion and diabetes (DM), hypertension (HTN), Patients with ischemic heart disease (IHD), renal involvement.

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To evaluate the relationship between albumin excretion and obesity, metabolic syndrome, dyslipidemia, hyperuricemia, tobacco intake and to see whether MA is early indicator of development of DM, Metabolic syndrome, and
To assess the utility of including Urine albumin creatinine ratio (ACR) estimation in routine health checkup clinic.

Materials And Method

This was a Cross sectional observational study carried out at a tertiary care hospital in eastern India between September 2016 and February 2018, to investigate the prevalence of MA and its association with risk factors in the urban population. The study protocol was reviewed and approved by the institutional ethical committee. The informed consent was waived due to the observational nature of the study.

A random group of population (n= 360) coming for executive health checkup as outpatients of a tertiary care hospital was screened for MA from an untimed urine sample. Then the ratio of albumin to Creatinine (ACR) was calculated and reported in mcg/mg. A standardized interview was carried out to collect information on demographic variable, family history, and medical history of hypertension, diabetes, cardiac problem, genito-urinary disease, medications used, history of smoking, exercise, pregnancy and other variables which may predispose to albumin urea.

The patients were instructed not to undergo physical exertion at least for 24 hrs before giving urinary sample. Patients with overt albuminuria, congestive cardiac failure, UTI, pregnant patients, menstruating ladies and patients having fever were excluded from this study. After completion of the interview, a detailed physical examination, laboratory studies and additional interviews were performed. Patients with fever, UTI, heart failure, history of heavy exercise, pregnancy, menstruation or vaginal discharge were excluded.

Statistical analyses

Data was analyzed using 2 x 2 contingency table and thus getting two tailed *p* value. At first univariate analysis was done. Then to exclude the effect of confounding diseases Multivariate logistic regression analysis was made.

Results

A total of 360 people, aged between 12 years and to 88 years, were screened. Of them 3 had macroalbuminuria, and were excluded. So 357 people were analyzed, out of them 262 (%) were male and 95 (%) were Female.

Of the 357 people analyzed, 50 people had microalbuminuria. Thus the prevalence of MA in general population coming for routine health up is 14%.

Out of the 262 men 14% had MA and out of 95 women 15% had MA. There was an increased tendency of microalbuminuria with increase in age. It was significant above age of 40 yrs (p 0.005). This is also true in both sexes individually. History of tobacco intake (smoke/ chew) was obtained in 87 of whom 9.2% had MA. MA was present in 28% of 67diabetic patients (p = 0.0002) and 18% among 68 pre diabetics (IFG/IGT) (p = 0.04). Hypertension was documented in 150 patients of whom 22% (p= 0.0002) had MA and of the patients with pre hypertension 12% (p= 0.0461) had MA. Prevalence of statistically significant increase in MA was found not only amongst diabetics and hypertensives but also amongst Pre diabetics and Pre hypertensives. Prevalence of MA among DM, pre DM and HTN, pre HTN increased with age. 13 patients had renal involvement as judged by raised creatinine / loss of corticomedullary differentiation and among them 46% had MA (p *=0.0045)*. Among 60 patients with ischemic heart disease 25% had MA. MA was found in 15% of 191 dyslipidemic patients, 24% of 50 hyperuricemic patients and 14% of 272

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overweight patients. In the patient subgroup with metabolic syndrome 24% had MA. (Table 1)

In our population (357) 111 had no history of DM, HTN, IHD or renal failure and still 7 had MA. Therefore 6.3% of people with no obvious risk factors showed presence of microalbuminuria. 48 person does not have DM, HTN, IHD, RF of their own but have family history any of those 4 risk factors. Among them 8.3% of people developed MA.

As expected diabetics, hypertensives, patients with IHD, metabolic syndrome, hyperuricemia and age> 40 yrs had increased risk of developing microalbuminuria (>20%) ($p < 0.05$).

There are many people who have more than one risk factors. So while doing univariate study there are many overlaps. If we do univariate analysis ignoring overlapping of diseases, we can say development of MA was significant in persons having DM, HTN, Metabolic syndrome, IHD, hyperuricemia and age> 40 yrs.($p< 0.05$).

Multivariate logistic regression analysis (table 2) showed MA was significantly associated with DM along with IGT, IFG and with HTN along with Pre HTN. There is significant development of MA in IHD and overweight.

Table 1: Association of MA and Risk factors

Risk factor		**MA+**	**MA-**	**P value**
Age	11-20 yrs (n=4) 21-30 yrs (n=26) 31-40 yrs (n=77) 41-50 yrs (n=80) 51-60 yrs (n=106) 61-70 yrs (n=52) 71-80 yrs (n=11) 81-90 yrs (n=1)	0% 7.69% 11.69% 8.75% 13.2% 25% 45.45% 0%	100% 92.31% 88.31% 91.25% 86.8% 75% 54.55% 100%	>40 yrs = 0.005*
IHD	(n=60)	25%	75%	0.007*
No IHD	(n=297)	12%	88%	
HTN	(n=150)	22%	78%	0.0002*
Pre HTN	(n=41)	12.2%	87.8%	0.0461
Normotensive	(n=116)	7.23%	92.77%	
IGT,IFG	(n=68)	18%	82%	0.0445
DM	(n=67)	28%	72%	0.0002*
Nondiabetic	(n=220)	9%	91%	
Obesity n over wt	(n= 272)	14%		0.55
Normal BMI	(n= 80)	16%		
Dyslipidemia	(n=191)	15.18%		0.722
Normal lipid	(n=166)	13.85%		
Hyperuricemia	(n=50)	24%		0.02*
Normal uric acid	(n=307)	12.38%		
Metabolic synd	(n=84)	23.8%		0.003*
No metabolic synd	(n=273)	10.99%		
Tobaco use	(n=87)	9.2%		0.14

Logistic Regression Model

$$\boldsymbol{P(MA = \text{"Y"}) = \frac{exp(\beta'.\widetilde{X})}{1 + exp(\beta'.\widetilde{X})}}$$

$$\boldsymbol{\beta'.\widetilde{X} = \beta_0 + \beta_1\beta_1 + \beta_2 x_2 + \ldots + \beta_k X_k}$$

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Table 2: Wald Statistics Response: MA

Factor	Chi-Square	d.f.	P
Sex	0.99	1	0.3209
DM	8.10	1	0.0044
HTN	4.75	1	0.0294
Hyperuricemia	1.86	1	0.1723
Creatinine	2.23	1	0.1356
Dyslipidemia	0.12	1	0.7333
IHD	3.60	1	0.0579
Obesity	3.20	1	0.0738
Family hx	1.45	1	0.2289
Total	29.00	9	0.0006

	Coef.
Intercept	-2.1924405
Sex=M	-0.3759309
DM=Y	0.9788111
HTN=Y	0.8380882
Hyperuricemia=Y	0.6056366
Creatinine=Raised	1.2143374
Dyslipidemia=Y	0.1141246
IHD=Y	0.7168659
Obesity=O	-0.7077353
Family hx=Y	-0.4024756

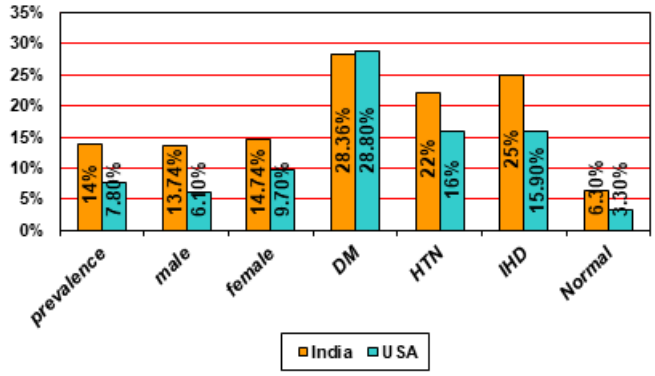

Figure 1: Comparison between US and our study

Discussion

In developed countries the prevalence of chronic kidney disease (CKD) has shown exponential growth, mainly due to T2DM and hypertension (14, 15). It is anticipated that developing countries will be facing a similar epidemic of CKD due to the rising prevalence of obesity and T2DM (16). Both CKD and CV disease share common risk factors, namely hypertension, diabetes, dyslipidemia, smoking and abdominal obesity (17,18). It has been suggested that there is also a hidden epidemic of cardiovascular (CV) disease in developing countries (19).

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CKD and CV disease are preventable by early recognition of patients at risk, and appropriate management. Micro- and macroalbuminuria are important predictors of renal disease and CV risk in hypertensives (20).

We have shown that the prevalence of excess urinary albumin excretion differs in the Indian population by sex, age, diabetes and hypertension as shown in US population in third NHANES study (32) In our study 6.3% people without any risk factors had MA, compared to 3.3% in the US population. These patients should be screened in future for development of hypertension, diabetes or renal disease, MA may be early warning for these diseases.

Data from the NHANES III and the EPIC-Norfolk studies (21,22), for instance, show women to have a higher prevalence of abnormal albuminuria if evaluated by ACR; This gender-related discordance between ACR and uncorrected UAC is clearly dependent on the fact that women excrete a lower amount of creatinine in their urine, secondary to a generally smaller muscle mass. In our study we had slight increase in prevalence of MA in females, though statistically insignificant.

In our study MA prevalence is lowest in young adults aged 11- 30 yrs and increases with age. The prevalence is significantly increases after age 40. In US Study the prevalence is lowest in young adults aged 20 to 39 years. Beginning after age 20 years, the prevalence of MA increases. In the US population, Non-Hispanic black and Mexican American race was independently associated with risk of albuminuria (ACR $\geq$ 30 mg/g) in adults 40 years and older after adjusting for the presence of diabetes, hypertension, cardiovascular disease, and chronic renal insufficiency.

The increasing prevalence of MA after young adulthood is explained in part by the increased prevalence of diabetes and hypertension with increasing age. However, this age-related increase in MA prevalence also was seen in the healthier population. It is unclear to what extent this finding in the healthier population is due to unmeasured concomitant disease, impaired glomerular function caused by the aging process, or the decrease in urinary creatinine excretion seen with increasing age [23,24].

In southern India 1425 type 2 diabetic patients were examined for prevalence of microalbuminuria in type 2 diabetes mellitus at a diabetes centre. Overall prevalence of microalbuminuria was 36.3% (95% confidence interval 33.8 to 38.9) (25)

Comparisons of our findings with results from other population-based studies is problematic, in part because of the variety measures that have been used to define MA when collection of 24-hour urine samples was not practical. Single untimed random urine specimens were collected during the conduct of the NHANES III to avoid formidable logistic difficulties, participant compliance problems, and uncertainties about the completeness and timing of urine collection. We use ACR to detect MA.

ACR has good reliability as a surrogate measure and has been recommended for routine screening purposes [26, 27]. We chose an ACR cut point of 30 mg/g because this criterion has been widely discussed for evaluation of persons with diabetes.

In the present study, prevalence of persons in the microalbuminuric range resulted in 13.74% (6.1% in US) of males and 14.74% (9.7% in US) of females so identified.

Currently, only 14% (7.9% in US) of the MA prevalence is explained by the combined effects of age, sex, race/ethnicity, history of diabetes or hypertension or cardiovascular disease, and level of serum creatinine.

In our study about 272 people had BMI > 23 and among them about 23.8% had MA. In Multivariate Logistic regression analysis they had approached significance (P= 0.07)

Serum uric acid (UA) is emerging as a novel risk factor for CV disease. In the study named “microalbuminuria and uric acid in healthy subjects” the author screened 900 healthy blood donors for serum UA, blood pressure (BP) and microalbuminuria (urinary albumin/creatinine ratio, ACR). In 848 participants the overall prevalence of excess ACR was 9.3% (9.7% of

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men, 7.5% of women, p=0.16). In a stepwise multiple regression model, Bellomo et al, had shown that correlation of serum UA to ACR remained significant, albeit attenuated (r=0.09, p=0.02), after adjustment for serum creatinine, total cholesterol, systolic and diastolic BP. The results can say serum UA to be an independent predictor of microalbuminuria (28)
In our study we have seen that about 24% of people had hyper uricemia. Though it became significant in univariate analysis (p=0.02) but lost its power in Multiple regression (P= 0.17). It may be due to the fact that h/o Allopurinol intake was missed out.
In a Korean study Hyo Sun Choi showed, the prevalence of microalbuminuria was 4.2% in the non-metabolic syndrome group (n = 5,902), and 14.4% in the metabolic syndrome group (n = 686). The odds ratio of microalbuminuria in the adults with the metabolic syndrome compared with those adults without the metabolic syndrome was 1.53 (1.13-2.07 95% CI). (29, 30)
In our study we also found that metabolic syndrome is significantly associated with microalbuminuria (p=0.003)

Limitations

This was single centre study. We have studied a specified subgroup of urban people attending health checkup clinic. As India is a country with huge population and diversity, so these results cannot extrapolate to the whole population.
We cannot exclude the possibility of inaccuracies in our estimates caused by false-positive outcomes since the measurement of a single untimed urine specimen cannot differentiate people with persistent MA and those with intermittent MA. Persistent MA may have more prognostic significance than intermittent MA. Physiological factors that can cause transiently elevated MA include dehydration, strenuous physical exercise, dietary protein, and acute fever [31]
Ours is a cross sectional study, not a longitudinal follow up study.
Although persistent MA is considered to be associated with progressive renal disease in patients with diabetes, we do not know.
Whether MA is indicative of a progressive process in nondiabetic populations. This question will need to be answered in longitudinal cohort studies. In addition, because the presence of MA was determined based on a single urine collection, it is not clear how many of these individuals would have persistent MA over time.
In this study, the higher frequency of microalbuminuria among women, defined by an ACR 30 µg/mg, was in part due to lower urine creatinine concentrations and not a higher urine albumin concentration. Creatinine is a metabolic byproduct of skeletal muscle creatine and phosphocreatine metabolism and is thus lower in subjects with lower muscle mass such as women or the elderly (33) Therefore, standardizing urine albumin concentrations to creatinine (*i.e.*, ACR) may underestimate microalbuminuria in subjects with higher muscle mass (men) and possibly in certain racial/ethnic groups, or overestimate it in subjects with lower muscle mass (women).

Conclusions

One in seven urban people have MA detected on routine health checkup, at a tertiary care centre, Besides T2DM and hypertension, MA is present in pre diabetics, and pre-hypertensives. In a small proportion it was found in people without any risk factors and may indicate diffuse endothelial dysfunction. ACR assessment should be included in all routine health checkup.

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