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Microalbuminuria and Its Correlation With Left Ventricuar Mass Index In Untreated Hypertensive Patients In Portharcourt, Southern Nigeria

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ABSTRACT

Hypertension is the commonest cardiovascular disease. Microalbuminuria is an early marker of end organ damage and its presence also indicates adverse cardiovascular outcome. We aim to identify the prevalence of microalbuminuria in newly diagnosed hypertensive patients in Port Harcourt and correlate their urinary albumin excretion with echocardiographically derived left ventricular hypertrophy using the left ventricular mass index. A cross sectional hospital based study of newly diagnosed, treatment naïve hypertensive patients at the cardiac clinic of the University of Port-Harcourt Teaching Hospital (UPTH). Demographic data was obtained; blood pressure, body mass index, dipstick urinalysis, urinary micro albuminuria, renal function, serum lipids and trans-thoracic echocardiography were assessed all the patients. 125 patients, age range 18 to 70 years, mean age 47.1±9.94years were recruited. Mean body mass index [BMI] was 27.28±2.82Kgm^{-2}, mean systolic blood pressure [SBP] was 164.53±18.53mmHg, mean diastolic blood pressure [DBP] was 104.30 ± 12.64 mmHg, mean total cholesterol [TCH] was 4.97±0.89mmol/L, mean LDL cholesterol was 3.22±0.95mmol/L, mean LVM was 231.29±77.45g and LVMI was 124.30±41.65 g/Kg/m^2. Mean Urinary Albumin excretion was 19.22±33.22mg/L. Prevalence of microalbuminuria was 32% and urinary albumin excretion correlated positively with the left ventricular mass (LVM), left ventricular mass index (LVMI), and LDL cholesterol. 71.2% of the subjects had left ventricular hypertrophy and among those with LVH, 52.21% had concentric LVH, 22.4 27.78% had eccentric LVH, and 23 23.01% had concentric remodeling. Micro albuminuria is highly prevalent in newly diagnosed hypertensives in Port Harcourt and correlates positively with left ventricular mass and left ventricular mass index.

Keywords: Microalbuminuria, Left ventricular hypertrophy, left ventricular geometry, left ventricular mass.

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INTRODUCTION

Hypertension is the commonest cardiovascular disease worldwide. Microalbuminuria is an early marker of end organ damage [and] its presence also indicates adverse cardiovascular outcome. Over the last 2 decades, following the first report by Parving et al[1] in 1974 that microalbuminuria (MA) was associated with essential hypertension (HTN) in non-diabetic individuals, interest for the study of MA in diabetics and non-diabetic patients with essential HTN has increased. This is especially so, from the 1990s when initial studies demonstrated the association of MA and other cardiovascular (CV) risk factors[1-4]. Thereafter, several small and large scale studies have identified MA as an independent risk factor and predictor of CV disease[5-8]. It has been demonstrated to predict future development of HTN and/or diabetes in the general population[9], but as well has been used as a prognostic factor in patients with CV and renal complications from HTN and diabetes[10-12].

Furthermore, studies have demonstrated the relationship of MA to subclinical end-organ damage in essential HTN and its association with factors for adverse CV risk[13]. Hence, Pedrinelli et al[14] in their review described MA as an integrated marker of cardiovascular risk in hypertension. Though, the pathophysiological mechanisms of microalbuminuria in essential HTN are not clear, it may reflect a systemic endothelial dysfunction (the Steno hypothesis) or may be associated with chronic low grade inflammation[15,16] on the one hand and on the other hand, as reported by Zeeuw and colleagues, it may represent an inherent variability of the vascular state as determined by microalbumin excretion at infancy that has been carried to adulthood[17].

Assessments of subclinical and clinically apparent end-organ damage are key elements in evaluation of patients with essential HTN. Detection of left ventricular hypertrophy (LVH) and geometric patterns is an integral part of the cardiovascular assessment of patients with HTN[18,19]. The American Diabetic Association (ADA) has also incorporated MA as an integral element of assessment of diabetic patients[20]. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: (The JNC 7 report)[18] and the European Society of Hypertension/European Society of Cardiology (ESH/ESC)[19]

Guidelines have recommended the assessment of MA in HTN. Studies have demonstrated the benefits of lowering urinary albumin excretion[2-22] and reduction in left ventricular mass and size[23-26] in hypertension treatment while those who do not achieve these have demonstrated potential adverse cardiovascular prognosis[27]. However, in our setting the routine assessment of this element of CV risk and disease is not practiced.

The aim of this study therefore, was to evaluate the prevalence of Microalbuminuria and its association with LVH and changes in the left ventricular (LV) geometry and to correlate urinary albumin excretion (UAE) and echocardiographically (Echo) derived left ventricular mass index (LVMI). This may highlight the importance of MA for assessment of cardiovascular risk and disease in our environment, and thus facilitate early interventions to prevent or reduce the development and progression of CV complications and adverse outcomes in essential hypertension.

MATERIALS AND METHOD

Study Population:

The study was a cross sectional hospital based study that was approved by the ethical committee of the institution. Patients with essential hypertension attending the general and medical out-patient clinics were referred to the cardiology unit of the hospital for recruitment into the study following a record of elevated blood pressure (BP) on two occasions two weeks apart. Detailed clinical history was taken to identify the duration of HTN, medications and co-morbid conditions. Only patients who have been recently diagnosed to have HTN (within the Last 3 to 6 months) that have not been on anti-hypertensive medications were included in the study. Other criteria for exclusion from the study were patients with positive dipstick for urinary protein, septicemic illness, pregnant women, obesity with body mass index (BMI) $\geq$ 30kg/m^2. Patients with diabetes mellitus and creatinine clearance $\leq$ 60µmol/min were also excluded.

One hundred and twenty five (125) patients aged 18 to 70years met the criteria for inclusion into the study within the study period of 11months. One hundred (100) apparently healthy non-hypertensive and non diabetic individuals, who met the criteria for inclusion to the study, were also randomly selected from hospital staff and patient relatives to evaluate the prevalence of MA among non-hypertensives/non-diabetics. Detailed physical evaluation was done, including anthropometric measurement of weight (wt) in kilograms (Kg) and height (ht) in meters (m) and BMI calculated as wt[Kg]/ht[m]^2.Hematological and biochemical assessment for hematocrit estimation, complete cell count, serum electrolytes, creatinine, urea, fasting serum lipid profile and fasting blood glucose were carried out. Urinary dipstick for protein, ketones and nitrites were also done.

Blood Pressure Measurement:

Blood pressure (BP) was measured with a standard sphygmomanometer (Accosson mercurial sphygmomanometer, England). Systolic and diastolic BP was taken at korokoff phases 1 and 5[21] respectively after a 5min. rest. The patient must not have taken coffee or amphetamine containing drink in the past 3 to 6hrs. Where korokoff phase 5 could not be

identified, phase 4 was taken as the diastolic BP. Average of two BP measurements taken 5-10mins apart with appropriate cuff size was taken. Blood pressures were classified using the Seventh Joint National Committee (JNV VII) classification for hypertension[18]. Blood pressure ≥140mmHg systolic and or 90mmHg diastolic was regarded as HTN. A repeat BP measurement was taken on the day of echocardiographic evaluation. Pulse pressure (PP) was calculated as Systolic BP (SBPSBP) - -Diastolic BP (DBP) and Mean arterial Pressure as DBP + 1/3PP.

Microalbuminuria Assessment:

Microalbuminuria [MA] was measured in patients who were negative for urinary protein, and with no evidence of urinary tract infection (UTI) ie, negative for urinary nitrite, normal complete blood cell count and without fever or other history suggestive of UTI or other septicaemic illness. Two non-consecutive samples were taken. First, a random spot urine sample on the day of first clinic attendance and an early morning (first void) urine sample on the day of Echocardiography. Samples were stored frozen for an average of two weeks before analysis.

Samples were analyzed by the immunoturbidimetry (anti-body based) method with a spectrophotometer (mini auto-analyzer – SFRI Sari Chemistry Analyzer, model BSA 300, Lieu dit Berganto Ind. France). Immunoturbidimetry assay reagents for urinary albumin (Randox Laboratory Ltd. UK.) with microalbumin calibration series, lot No: 1198IT(729MA-733MA) was used.

Differences in absorbance wave length were read against standard MA concentrations in a standard microalbumin calibrator curve using a semi- logarithmic graph[22]. MA concentrations between 20-200mg/L on two occasions were taken as significant. This is equivalent to 30-300mg of urinary albumin excretion in 24hrs[28].

Echocardiographic Assessment:

Echocardiography (Echo) was done with an ALOKA Echocardiographic machine (model SSD-4000, ALOKA CO. LTD. Tokyo Japan) with a standard cardiac probe.

Echo was done with the patient lying in the left lateral decubitus position. Standard views were taken from the left parasternal long and short axes and apical views and measurements carried out according to the ACC protocol. 2D targeted M-mode measurements of the left ventricular dimension were taken at end diastole. The interventricular septal thickness (IVSd), left ventricular internal diameter (LVIDd) and left ventricular posterior wall thickness (PWTd) at end diastole just beyond the tip of the mitral valves in the left parasternal long axis view[29,30] were measured. The American Society of Echocardiography (ASE) recommendations for M-mode measurement of the left ventricle were followed[29].

The LVM was calculated with the cube (Teicholz) method using the ASE formula modified by Devereux[31]. $LVM(g) = 0.8(1.04\ (1VSd + LVIDd + PWTD)^3 + 0.6$

Where

IVSd = Interventricular septal thickness in diastole

PWTd = Posterior wall thicken in diastole

LVIDd = LV Internal Diameter in diastole.

The LVM was indexed to the Body Surface Area (BSA) to give the Left Ventricular Mass Index (LVMI). Increased LVM was taken at LVM ≥ 162g for females and ≥ 224g for males. And increased LVMI was taken as LVMI ≥ 95 for females and ≥ 115 for males[27].

Relative wall thickness (RWT) was calculated as 2 x PWTd/LVIDd and increased RWT was taken as RPWT ≥ O.45.

The LV geometry was classified based on the evaluations of LVMI and RPWT as follows:

Normal geometry – Normal LVMI and RPWT.

Concentric remodeling – Normal LVMI and increased RPWT.

Eccentric hypertrophy – Increased LVMI and RPWT< 0.45

Concentric hypertrophy – Increased LVMI and RPWT greater or equal to 0.45.

Statistical Analysis:

Data was analyzed using the statistical package for social sciences (SPSS) version 17.0. Prevalence results were expressed in percentage; continuous (non-categorical) variables were expressed in mean ± standard deviation and compared by the independent student t-test. Categorical variables were compared with the chi-square test and Pearson`s correlation coefficient test was used to measure the association between UAE and LVMI.

RESULTS AND DISCUSSION

Clinical characteristics of patients and controls

One hundred and twenty five (125) patients (45 males and 80 females) and one hundred (100) controls (37 males and 63 females) participated in the study. The mean age of the study population and control population were 47.16±9.94years and 47.09±9.93years respectively. The mean body mass index (BMI) of the patients and control population were 27.28±2.82Kgm^{-2} SD and 26.79±2.72 respectively and were not different statistically. The mean systolic and diastolic blood pressures [SBP, DBP] were 164.53±18.53mmHg and 104.30±12.64mmHg respectively.

The mean total cholesterol [TCH] was 4.97±0.89mmol/L, mean LDL cholesterol was 3.22±0.95mmol/L, mean Left Ventricular Mass [LVM] was 231.29±77.45g SD and mean left ventricular mass index [LVMI] was 124.30±41.65 g/Kg/m^2. Mean Urinary Albumin excretion was 19.22±33.22mg/L SD.

The Prevalence of microalbuminuria was 32.0% in the study subjects and 6.0% in controls while mean urinary albumin excretion were 19.22+ 33.21md/L and 5.30+9.33mg/L in the study population and control respectively. The urinary albumin excretion in study subjects correlated positively with the left ventricular mass (LVM), left ventricular mass index (LVMI), and LDL cholesterol [correlation co eff =].

A total of 89 [71.2%] of the subjects had left ventricular hypertrophy, 47.2% had concentric LVH, 22.4% had eccentric LVH, and 20.80% had concentric remodeling. The study subjects had significantly higher waist circumference compared with controls 92.80±9.14 Vs 89.062±9.56, p=0.003) and office blood pressure (BP) indices; SBP (p=0.000), DBP (p=0.000), Pulse pressure (PP) (p=0.000) and mean arterial pressure (MAP) (p=0.000). The prevalence of microalbuminuria (MA) was 32.0% among the hypertensive patients and 6.0% in the control population. This is as shown in table 1.

Microalbuminuria and Clinical characteristics of the patients

Table 2, compares the clinical characteristics of the hypertensive patients with and without MA. The hypertensive patients with MA had significantly higher mean age (p=0.002), SBP (p=0.000), DBP (p=0.000), PP (p=0.012) and MAP (p=0.000). The mean serum uric acid, fasting lipids and anthropometric measurements were not statistically different.

In table 3, the echocardiographic characteristics of the patients are shown. The hypertensive patients with MA had statistically significant higher mean LVM and LVMI than those without MA. They had lower mean ejection fraction (EF) and fractional shortening (FS) than the patients without MA, but this was not statistically significant.

Relationship of Urinary Albumin Excretion with LVH and LV Geometry

Table 4 and figures 1 and 2 shows the correlation of urinary albumin excretion (UAE) with LVM and LVMI. Urinary Albumin Excretion [UAE] had a significant positive correlation with LVM (p=0.000), and LVMI (0.000). As shown in figures 1 and 2, UAE has a linear relationship with LVM and LVMI respectively. 89 patients (71.2%) had developed LVH by Echo assessment of LVMI table 5. Out of the 40 patients with MA, 33 (82.5%) had LVH as against 56(65.9%) of 85 patients without MA and only 7(17.5%) of those with MA retained normal LVMI as against 29(34.1%) of those without MA.

Figure 3 shows the mean UAE with respect to the different left ventricular geometric patterns. The hypertensive patients with concentric left ventricular hypertrophy had higher mean UAE than those with normal geometry, eccentric hypertrophy or concentric remodeling.

Table 1: Anthropometric and Clinical Characteristics of Subjects and Controls

Clinical Characteristics	Patients	Controls	t	P
Study population	125	100		
Males	45	37		
Females	80	63		
MA	40(32.0%)	6(6.0%)		
UAE	19.22±33.22	5.30±9.33		
Mean Age	47.16±9.93 SD	47.09±9.93 SD	0.053	0.096
Mean Weight	75.01±10.04SD	76.52±10.30SD	-1.107	0.269
Mean BMI	27.28±2.82 SD	26.79±2.72 SD	1.317	0.189
Mean WC	92.80±9.14 SD	89.06±9.56 SD	2.985	0.003
Mean SBP	164.53±18.53SD	117.10±9.36SD	23.322	0.000
Mean DBP	104.30±12.63SD	74.60±6.25 SD	21.487	0.000
Mean PP	60.11±15.09 SD	42.60±8,96 SD	10.240	0.000
Mean MAP	120.21±15.89SD	88.87±6.22 SD	18.606	0.000

Table 2: Relationship of Microalbuminuria and Clinical Correlates

Clinical Correlates	Microalbuminuria		t	p value
	YES	NO		
	Mean ± SD	Mean ± SD		
Age	51.20±19.50	45.26±9.55	3.234	0.002
SBP	177.30±19.50	156.52±14.69	5.984	0.00
DBP	111.15±13.14	101.08±11.07	4.461	0.00
PP	65.05±16.13	57.79±14.09	2.564	0.01
MAP	128.07±16.67	116.52±14.16	4.05	0.00
UA	424.98±144.27	404.71±128.17	0.79	0.43
TG	1.27±0.58	1.31±0.60	-0.36	0.71
TCH	4.97±0.87	4.96±0.92	0.05	0.96
HDL	1.19±0.39	1.17±0.93	0.18	0.86
LDL	3.22±1.02	3.23±0.93	-0.04	0.96
BMI	27.25±2.91	27.30±2.80	-0.09	0.93
WC	94.58±9.30	91.96±9.00	1.50	0.14

YES-MA present, NO-no MA, SD-standard deviation, WC – waist circumference

Table 3: Relationship of Microalbuminuria and Echocardiographic Indices

Echo Indices	Microalbuminuria		t	p value
	YES	NO		
	Mean ± SD	Mean ± SD		
LVM	282.70±90.22	207.09±56.78	5.702	0.000
LVMI	152.53±48.83	111.02±29.92	5.853	0.000
EF	65.57±9.26	67.22±9.37	-0.923	0.358
FS	36.56±6.94	37.74±7.48	-0.836	0.405

YES-MA present, NO-no MA, SD-standard deviation

EF = Ejection Fraction

FS =Fractional Shortening

Table 4: Correlation of UAE and LVM and LVMI

LVM and LVMI	Urinary Albumin Excretion (UAE)	
	R	p- value
LVM	0.328	0.000
LVMI	0.314	0.000

LVM = Left Ventricular Mass

UAE = Urinary Albumin Excretion

LVMI = Left Ventricular Mass Index

Table 5: Relationship of MA and LVH Based on LVMI in Patients

LV Assessment	Microalbuminuria		Total (%)
	YES	NO	
LVH	33(82.5%)	56(65.9%)	89(71.2)
No LVH	7(17.5%)	29(34.1%)	36(28.8)
Total	40(100.0)	85(100.0)	125(100.0)

YES – MA present, NO – No MA.

MA = Microalbuminuria; LVH = Left ventricular hypertrophy; LVMI = Left ventricular mass index

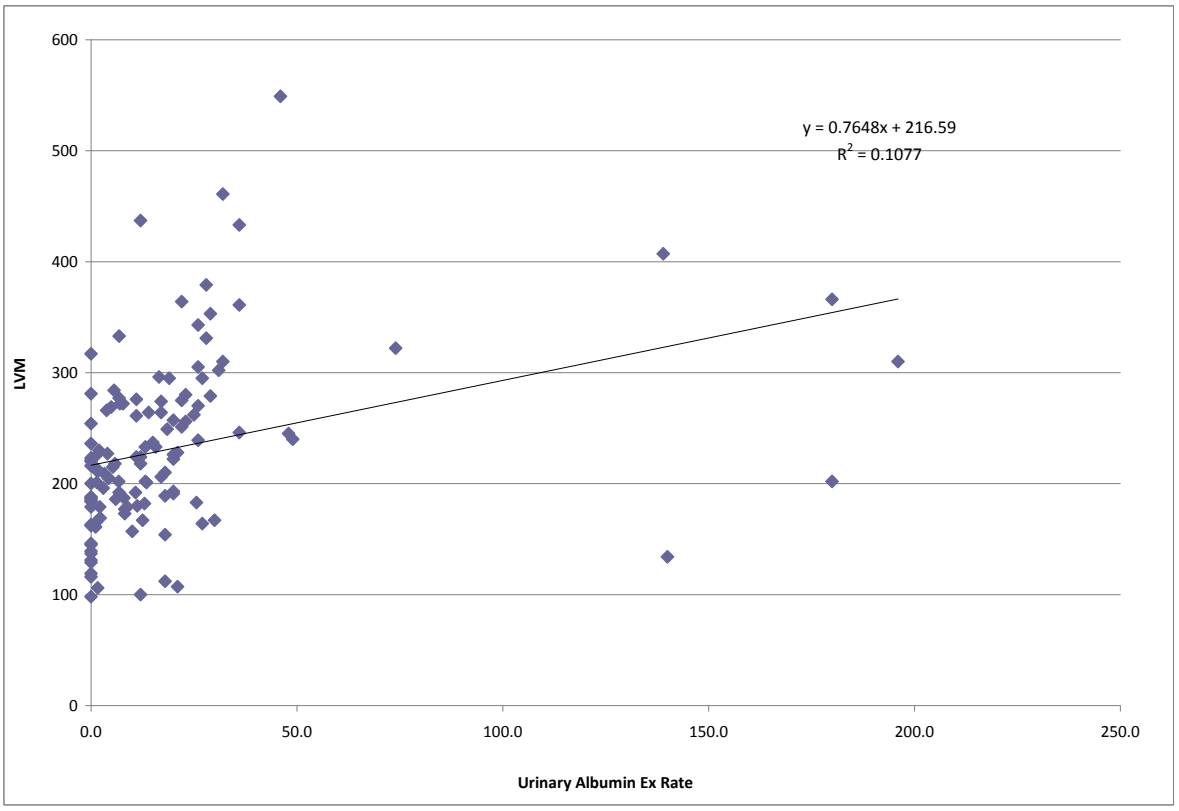

Figure 1: Graph; showing the correlation of Urinary Albumin Excretion (UAE) and Echo derived LVM

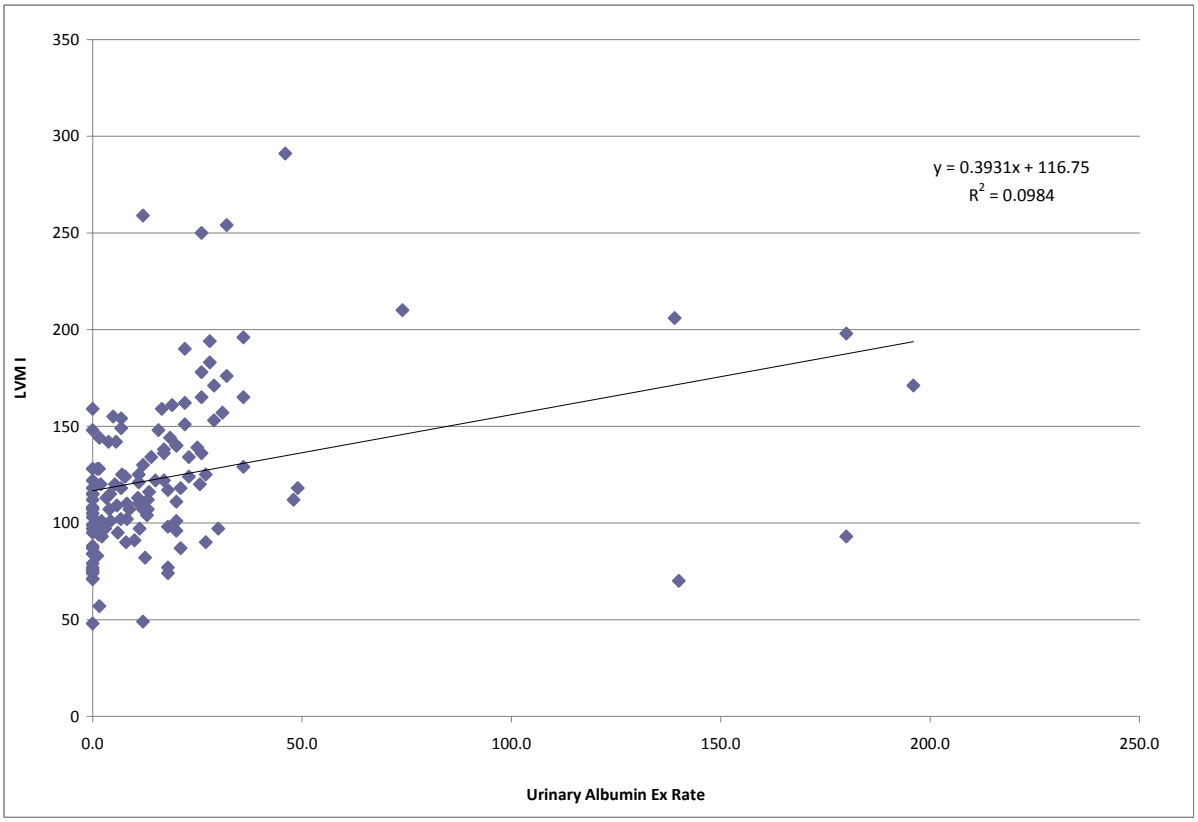

Figure 2: Graph; showing the correlation of Urinary Albumin Excretion (UAE) and Echo derived LVMI

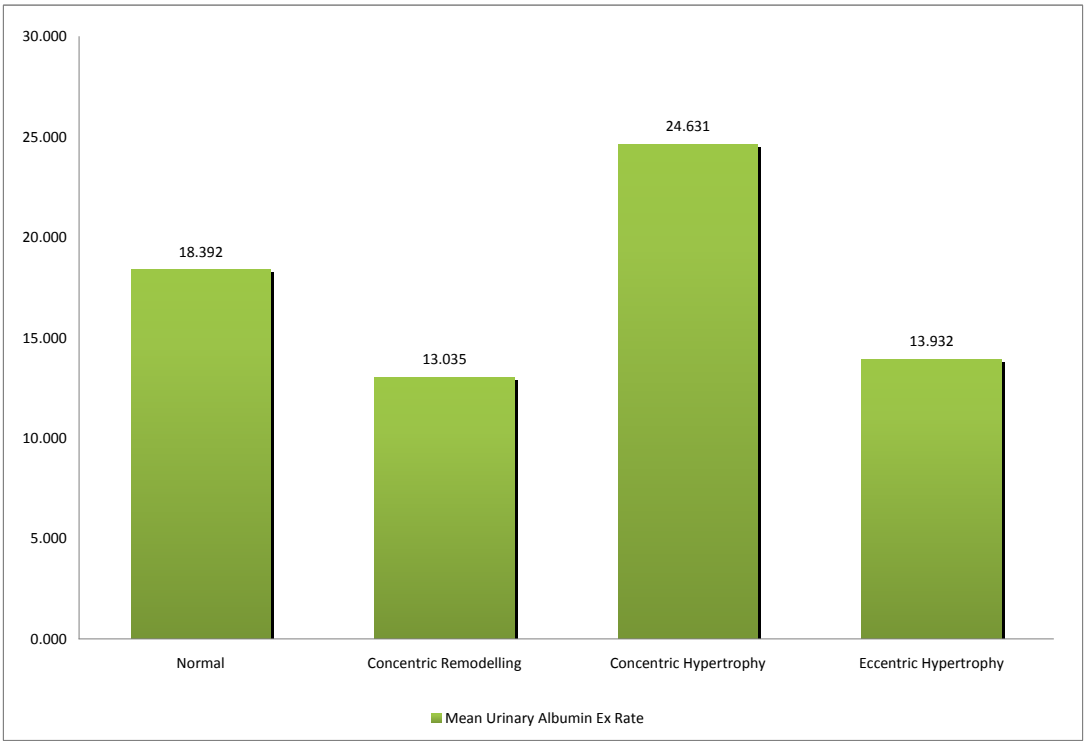

Figure 3: Relationship of MA and LV Geometric Patterns

DISCUSSION

The principal findings in this study were that microalbuminuria [MA] is common among hypertensive patients in our environment occurring in 36% of the hypertensive patient

studied and it is associated with development of left ventricular hypertrophy (LVH) and changes in left ventricular (LV) geometry, especially concentric hypertrophy. Urinary albumin excretion (UAE) increases linearly with increases in left ventricular mass (LVM) and left ventricular mass index (LVMI). Several large scale studies have demonstrated that MA is independently linked with risk for cardiovascular disease and complications in hypertensive patients[28-30]. There are also clear indications of its association with other factors for cardiovascular risk. Accumulating evidence indicates a close and parallel relationship between MA and cardiovascular events in patients with essential hypertension. MA confers a four-fold increase in risk of ischaemic heart disease amongst hypertensive patients[31]. In large and small scale studies, MA has been associated with fatal and non-fatal stroke, recurrent stroke, cardiovascular death and all-cause mortality as well as non-cardiovascular deaths [12,33].

In fact, in the HOPE trial, the risk for a composite end point of cardiovascular death, non-fatal stroke and non-fatal MI began to increase as the Albumin/creatinine ratio (ACR) increased above 1.9mg/g creatinine. The risk was 6% higher for every 4mg/g increase in the Albumin/creatinine ratio[12]. The Framingham study[33] further showed that UAE even at levels well below the current threshold for MA confers increased risk for CVD and mortality in non-

hypertensive and non-diabetic individuals. The findings in this study of a black population is in keeping with similar findings in Caucasian popilations and have important clinical implications in patients with hypertension in PortHarcourt. The high prevalence of microalbuminuria, increased left ventricular mass and left ventricular hypertrophy in these treatment naïve patients indicates significant target organ damage in these untreated hypertensives and confers excessive cardiovascular disease risk on them. This is in keeping with findings in previous studies on African-Americans which showed that black hypertensive patients have greater target organ damage than whites for the same grade of hypertension and are more likely to die from its complications[34] and imposes a great burden on health care providers in our setting. These findings may suggest the need for MA assessment in newly diagnosed hypertensive patients to facilitate early therapeutic interventions.

The prevalence of MA and LVH in this treatment naïve hypertensives of purely black Nigerian population was 32.0% and 71.2% respectively. The hypertensive patients with MA were more likely to have changes in their LV geometry, especially concentric LVH, and the patients with JNC-7 stage 2 HTN more frequently had MA. Data from this study also showed that 82.5% of the patients with MA had LVH compared with 65.9% of those without

MA, and that 97.5% of the patients with MA had developed changes in their LV geometry. Of these, 72.5% had developed concentric LVH compared with 20% of those without MA. This significantly influences the approach to CV assessment and choice of treatment of hypertension in this black population in Port-Harcourt, South-South Nigerian.

The association of MA with LVH and abnormal left ventricular geometry may explain some of the cardiovascular risk and prognostic significance of MA. Again, LVH and abnormal LV geometry are important predictors of outcome and important tools in the risk stratification of hypertensive patients[18,19]. Furthermore, studies have demonstrated the association of MA with markers of endothelial dysfunction and chronic inflammation leading to increased wide spread systemic and renal vascular permeability and thrombus formation that are the pathophysiologic events in CVD[15,16]. This integrated relationship between MA and the left ventricular changes may explain a common pathway for many adverse events in the heart and kidney in hypertensive patients.

This study showed that males and hypertensive subjects with advanced age have higher prevalence of abnormal LV geometry and MA as demonstrated and hence a higher incidence of adverse cardiovascular outcome and is similar to findings in African American [34]. Studies have demonstrated the benefits of lowering urinary albumin excretion[35-37] and reducing left ventricular mass and size[38-41] in hypertension treatment. Also, Muiesan and colleagues[42] demonstrated the potential adverse cardiovascular prognosis in patients who do not achieve left ventricular mass reduction during hypertension treatment.

Therapeutic strategies to reduce blood pressure, as well as MA and LVH are available in clinical practice and would contribute to reduction of total cardiovascular disease burden. This could be achieved by Angiotensin converting enzyme inhibitors (ACEI) or Angiotensin receptor

blockers (ARB), thiazide diuretics, beta blockers and dietary salt reduction[36-43]. ACEIs, ARBs and beta blockers are particularly important for their beneficial effect on humoral factors that mediate left ventricular hypertrophy and albuminuria in hypertension.

CONCLUSIOON: From the results of the study [Despite the above limitations,] we conclude that the prevalence of MA is high in our hypertensive population and is associated with other factors of CV disease and risk such as dyslipidemia, obesity and left ventricular hypertrophy. There was is also evidence that UAE had a linear relationship with LVM and LVMI and a correlation with other markers of CV risk, disease and complications such as LVH and LV geometry that are routinely assessed in our clinics, and also that UAE has a linear relationship with LVM and LVMI.

Therefore based on these findings, we recommend that the routine assessment of MA may be incorporated into the evaluation of patients with essential HTN for better overall CV risk assessment to guide appropriate care and treatment our black population in Port-Harcourt, South-South Nigeria.

LIMITATION:

The study has its limitations. Though, an average of two measurements of UAE were taken, there was no correction for potential variability in urine concentration. The duration of HTN from self-reported history may not be accurate, as the parameters measured in the study are affected by both duration and degree of high blood pressure. Again a larger sample size may have added more power to the study.

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