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Albuminuria Predicts Kidney Function Outcome in Egyptian Essential Hypertensive Patients

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Abstract

Background and Aims: Hypertension is both a cause and effect of renal impairment and its treatment influences kidney function outcome, interests in the study of albuminuria in hypertensive patients has grown as it may represent a useful and relatively inexpensive clinical tool for the identification of hypertensive patients at higher risk for developing early renal impairment. In Egypt, hypertension is one of the most important causes of end stage renal disease (ESRD). The aim of the work is to identify albuminuria in Egyptian essential hypertensive patients, and its relation with kidney function outcome.

Methods: Two hundred and forty one essential hypertensive patients, were included in a cross-section study for the presence of albuminuria and its relation to estimated glomerular filtration rate (eGFR); their history of hypertension ranges from 12-240 months with a mean of 75±54 (aged 48±11 years, range 20 – 76 years) any patient with doubtful history of essential hypertension were excluded from the study, patients included in the study were 148 (61%) males and 93 females, their mean body mass index was 27±5 kg/m2.

Results: Prevalence of normoalbuminuria was 59%, microalbuminuria 31%, and macroalbuminuria 10%. eGFR was significantly decreased in microalbuminuria and macroalbuminuria groups, on further analysis this reduction in eGFR was not related to severity of hypertension but to its duration. There was a significant increase in the duration of history hypertension in eGFR < 60 ml/min/1.73 m2 in comparison to eGFR > 60 ml/min/1.73 m2 in all groups (Normo, Micro and Macroalbumiuria). There was no significant difference eGFR between controlled and uncontrolled groups (either by MDRD or Mayo clinic formula).

Conclusions: Albuminuria is a risk marker for prediction of the progression of nephropathy in Egyptian essential hypertensive patients and may reflect hypertensive injury to the kidney.

Keywords: Hypertension, Albuminuria, Glomerular Filtration Rate, Kidney Function Outcome

Introduction

Hypertension is both a cause and effect of renal impairment and its treatment influences renal outcomes (1). The conventional method of detecting renal damage in hypertensive patients by measurement of blood urea nitrogen, creatinine and proteinuria are relatively insensitive and show only abnormalities when the disease process is advanced. However, there is a considerable interest in the quantitative measurement of albuminuria to detect subtle effects of hypertension on the kidney (2).

Essential hypertension produces clinical proteinuria

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and a significant reduction in renal function in 5 – 15% of patients (3). The pathophysiological mechanisms underlying the presence of microalbuminuria are still controversial: from one hand it might be the result of intrarenal hemodynamic changes brought about by increased systemic blood pressure, and from the other hand it might be a marker of capillary leakiness at the glomerular level and reflect more generalized atherosclerotic vascular damage (4).

Increased urinary excretion of albumin has been found in a relatively large number of patients with essential hypertension (3, 5, 6). Experimental studies offer a solid support to the concept that albuminuria is a marker of endothelial dysfunction in the kidneys. Microalbuminuria is also a feature of human hypertension (7).

Recent observations in the Framingham Heart Study cohort have shown that a subtle increase in urinary albumin excretion antedates the clinical outset of arterial hypertension in healthy individuals in the general population (8). Microalbuminuria may lead to renal insufficiency in essential hypertensive patients and its detection can help physicians to select specific antihypertensive drugs to lower or ameliorate it and, thus, prevent undesirable outcomes (9, 10).

In Egypt, hypertension is one of the most prevalent causes of end stage renal disease (ESRD) and is responsible for 29.7% of cases of ESRD in Cairo, 28.9% in Lower Egypt governorates, 25% in Upper Egypt governorates, 27.3% in Suez Canal governorates, and 26.5% in border governorates (11). So, interest in the study of albuminuria becomes of utmost importance as it may represent a useful and relatively inexpensive clinical tool for the identification of hypertensive patients at higher risk for developing early renal impairment.

The aim of the work is to investigate the prevalence of albuminuria, in essential hypertensive patients attending the Outpatient Clinic, El-Minia University Hospital, Egypt, its relation with severity, duration of hypertension and kidney function outcome.

Materials and Methods

This cross-sectional study was done from July 2008 to April 2009 and involved essential hypertensive patients attending the Outpatient Clinic, Medicine Department, El-Minia University Hospital, Egypt. It included 241 essential hypertensive patient, 148 (61%) of them were males, their age was 48±11 (range 20-76) years, inclusion criteria were patients who are hypertensive and attend the outpatient clinic by appointment and are receiving antihypertensive drugs regularly. Their history of hypertension ranges from 12-240 (mean 75±54) months.

Any patient with doubtful history of essential hypertension or history suggestive of other glomerular lesion was excluded from the study, exclusion criteria were any patients with clinical or laboratory evidence of hepatic or thyroid disease as well as females on oral contraceptive pills and diabetic patients, any symptoms of a urinary tract infection as pain on passing urine, passing urine frequently, or leucocyturia > 5 per high power field, were excluded from the study, microscopic hematuria, dysmorphic RBCs, fever and heavy exercise as well as any abnormality in serum electrolytes or renal ultrasonography were also excluded from the study. So the total number of patients excluded from the study was 59 patients. After giving verbal consent to participate, a questionnaire was completed including their smoking status, current medical illnesses, and their family history of hypertension and cardiovascular disease. Duration and onset of hypertension, as well as their recent anti dyslipidemic drugs were also recorded.

Prior to blood pressure (BP) measurement all patients were asked to evacuate their urinary bladder, and rest in a quiet comfortable place in the supine position for at least 5 minutes. Food, cigarette smoking, tea and coffee were prohibited for at least 2 hours prior to BP measurement.

BP was measured on the right arm with a mercury sphygmomanometer (cuff size, 12.5x40 cm) by a physician. Disappearance of Korotkoff's sounds (phase V) was the criterion for Diastolic Blood Pressure (DBP). Mean arterial Pressure was calculated as diastolic blood pressure plus one third of pulse pressure. Body weight and height were measured also for participants, body mass index (BMI) was calculated with the following formula:
BMI=weight (kg)/height (m^2)

First voided morning urine sample was obtained from each patient for the assessment of albuminuria by enzyme immunoassay and urinary creatinine g/dl (12). Venous blood sample was drawn after complete aseptic technique for laboratory evaluation of blood urea nitrogen (BUN), creatinine, electrolytes, serum albumin, total cholesterol and triglycerides, using an automated clinical chemistry dimension ES and complete blood count using an automated cell coulter Sysmex NE.

Normo, Micro and Macroalbuminuria

The subjects were then divided into three groups:

1. Normoalbuminuria, < 30 mg albumin/ g. Creatinine: 142 (59%) patients
2. Microalbuminuria, 30 – 300 mg albumin/ g. Creatinine: 74 (31%) patients
3. Macroalbuminuria, > 300 mg/ g. Creatinine: 25 (10%) patients

Adequacy of BP control was defined according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7 Report) (13). Hyperlipidemia and the adequacy of lipaemic control were defined according to the Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (14). Obesity and overweight were defined according to World Health Organization (WHO) Guidelines (15).

Estimation of glomerular filtration rate (GFR)

GFR was estimated using two different formulae, MDRD (16) and Mayo Clinic (17) formulae.

Statistics

Statistical analysis was performed by using commercially available statistical software (minatab 15). Quantitative variables were compared using unpaired t-test and one way ANOVA test. Qualitative variables were compared using Chi square and test of proportion. Data were tested for normality and it was found that data were normally distributed. The P value of less than 0.05 was considered as statistically significant.

Results

Two hundred and forty one hypertensive patients (aged 48±11 years, range 20-76 years) were included in a cross-section study for the presence of albuminuria. Among these 241 patients, mono antihypertensive therapy was prescribed for 101 patients (42%) while 93 (39%) patients were using two drugs, 37 (15%) took three drugs, and 10 patients (4%) took four drugs the mean of the total antihypertensive drugs was 2±0.8. Table 1 summarizes the clinical and the biochemical characteristics in all patients.

The levels of BUN and serum creatinine were higher in macroalbuminuria group when compared to normoalbuminuria group (17±4 mg/dl and 1.6±0.4 mg/dl versus 10±3 and 1.4±0.4 mg/dl). Also, there was a significant decrease of eGFR in macroalbuminuria group as compared to normoalbuminuria group (Table 2). There was a significant increase in the duration of hypertension in macroalbuminuria in comparison to microalbuminuria and normoalbuminuria (Table 2). Moreover, patients were classified to controlled hypertensive patients (14%) and uncontrolled hypertensive patients according to JNC 7 Report (13); there was no significant difference eGFR between controlled and uncontrolled groups (Table 3).

On further analysis of normoalbuminuria group,

Table 1. Clinical and biochemical characteristics of all patients

	All Patients
Number of patients	241
Age (years)	48±11
Males	148 (61%)
Females	93 (39%)
BMI (Kg/m^2)	27±5
MAP (mmHg)	105±13
Total antihypertensive	2±0.8
CCB	152 (63%)
ACEi	108 (44%)
Diuretics	52 (22%)
α blockers	17 (7%)
ARBs	29 (12%)
β blocker	74 (31%)
Statin use	98 (41%)
Serum Albumin (g/dl)	4±2
Hemoglobin (g/dl)	14±5
Hematocrit (%)	40±5
Cholesterol (mg/dl)	207±44
History of HTN (month)	75±54
eGFR MDRD (ml/ min/1.73m^2)	52±18
eGFR Mayo Clinic (ml/ min1.73m^2)	70±26

MAP, Mean arterial blood pressure; **CCB**, Calcium channels
Blockers; **ACEi**, Angiotensin converting enzyme inhibitors;
ARBs, Angiotensin receptor blockers; **eGFR**, estimated glomerular filtration rate.

we found eGFR < 60 ml/min/1.73 m2 in 87 patients and eGFR > 60 ml/min/1.73 m2 in 55 patients. There were significant differences in serum albumin, hemoglobin and hematocrit between both subgroups as well as significant increase in the duration of hypertension between two subgroups in terms of eGFR in all groups (Table 4).

Discussion

We found significant differences between eGFR in macroalbuminuria, microalbuminuria and normoalbuminuria groups. On further analysis, these differences were not related to severity of hypertension but were related to duration of hypertension.

Jalal et al (2) founded microalbuminuria in 37.5% of patients with hypertension, possibly pointing toward the subclinical changes occurring in the glomeruli of these patients. While Bigazzi et al (3), Giaconi et al (18) and Pedersen et al (19) reported that the prevalence of microalbuminuria is not well established and it may vary from 15 – 100 percent. This variation between the current study and other studies is probably due to difference in the age, duration of hypertension and coexistent renal disease in their study populations.

Pontremoli et al (20) reported that Microalbuminuria was present in 53 subjects (6.7%) and Perticone et al (7) concluded that albuminuria may contribute to renal impairment independently of inflammation and hemodynamic endothelial dysfunction in hypertensive subjects.

In Egyptian essential hypertensive patients who attend the out patients Clinic at El-Minia University Hospital the prevalence of normoalbuminuria was 59% of patients, microalbuminuria 31% and macroalbuminuria was 10%. Similarly, in the Third National Health and Nutritional Examination Survey (NHANE III) of the US population, using the urinary albumin – creatinine ratio (UACR) to identify microalbuminuria in non-diabetic hypertensive, the prevalence of microalbuminuria was found to be 16% (21) and it was 22% in the EPIC-Norfolk population

Table 2. Clinical and biochemical characteristics of the three groups

	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
Number of patients	142 (59%)	74 (31%)	25 (10%)
Age (years)	46±11	50±11*	52±11*
Males	95 (67%)	42 (57%)	11 (44%)
Females	47 (33%)	32 (43%)	14 (56%)
BMI Kg m^2	27±5	28±5	27±6
MAP (mmHg)	105±12	106±13	110±17
Antihypertensive	1±0.5	2±0.5*	3±0.5*#
CCB	76 (54%)	55 (74%)	21 (84%)
ACEi	46 (32%)	47 (64%)	15 (60%)
Diuretics	8 (6%)	30 (41%)	14 (56%)
α blockers	5 (4%)	2 (3%)	10 (40%)
ARBs	19 (13%)	6 (8%)	4 (16%)
β blocker	29 (20%)	28 (38%)	17 (68%)
Statin use	58 (41%)	28 (38%)	12 (48%)
Serum Albumin (g/dl)	4.2±3	3.9±3	3.3±0.5
Hemoglobin (g/dl)	13.4±1.6	13.8±1.5	14±1.6
Hematocrit (%)	40±5	41±4	41±5
Cholesterol (mg/dl)	200±44	214±42	230±40
History of HTN (month)	38±16	107±24*	192±29*#
eGFR MDRD (ml/ min/1.73m^2)	69±24	62±14	46±14*#
eGFR Mayo Clinic (ml/ min1.73m^2)	72±28	72±20	55±24*#

* Significant *vs.* Normoalbuminuria.
# Significant *vs.* Microalbuminuria.
MAP, Mean arterial blood pressure; **CCB,** Calcium channels blockers; **ACEi,** Angiotensin converting enzyme inhibitors; **ARBs,** Angiotensin receptor blockers; **eGFR,** estimated glomerular filtration rate.

study conducted in the UK (22). The prevalence of microalbuminuria was also similar in other cross sectional studies in other populations. For example, of 439 non-diabetic hypertensive randomly selected from 7708 Turkish people living in Ankara, 18.9% had microalbuminuria as determined by the Micral® test (23).

In the Newcastle Heart Project (24) 14.4% of 598 south Asian non-diabetic hypertensive had microalbuminuria, as determined by UACR. Higher prevalence have been reported in more elderly populations and those with more severe and a longer duration of hypertension. For example, a large survey carried out by general practitioners in Germany involving 11343 non-diabetic hypertensive showed that microalbuminuria assessed by immunoassay test strips, occurred in 30% of the Patients (25), and, in a study of 731 Japanese subjects assessed by UACR, microalbuminuria occurred in 26.2% (26).

On the contrary, lower occurrences of micro-albuminuria have been found in younger patients and those with less severe and a shorter duration of

Table 3. Clinical and biochemical characteristics of controlled and uncontrolled hypertensive patients

	Controlled	Uncontrolled	P Value
Number of patients	33 (14%)	208 (86%)	
Age (years)	44±12	49±11*	0.01
Males	18 (55%)	130 (63%)	0.44
Females	15 (45%)	78 (37%)	0.44
BMI Kg m^2	28±4	28±6	1.00
MAP (mmHg)	88±6	108±11*	0.001
Antihypertensive	1.8±0.9	1.8±0.8	1.00
CCB	21 (63%)	131 (63%)	1.00
ACEi	17 (52%)	91 (44%)	0.45
Diuretics	10 (30%)	42 (20%)	0.25
α blockers	2 (6%)	15 (7%)	0.80
ARBs	2 (6%)	27 (13%)	0.14
β blocker	7 (21%)	67 (32%)	0.16
Statin use	13 (39%)	85 (41%)	1.00
Serum Albumin (g/dl)	3.5±0.3	4±0.3*	0.001
Hemoglobin (g/dl)	14±2	14±2	1.00
Hematocrit (%)	40±4	40±5	1.00
Cholesterol (mg/dl)	210±57	207±42	0.71
History of HTN (month)	87±61	74±53	0.20
eGFR MDRD (ml/min/1.73m^2)	50±13	52±18	0.54
eGFR Mayo Clinic (ml/ min1.73m^2)	68±21	71±27	0.54
Normoalbumiuria	20 (61%)	122 (58%)	1.00
Microalbumiuria	8 (24%)	66 (32%)	0.42
Macroalbumiuria	5 (15%)	20 (10%)	0.35

* $p < 0.05$

MAP, Mean arterial blood pressure; **CCB**, Calcium channels blockers; **ACEi,** Angiotensin converting enzyme inhibitors; **ARBs,** Angiotensin receptor blockers; **eGFR,** estimated glomerular filtration rate.

hypertension. For example, microalbuminuria was reported in 14.4% of 5359 non-diabetic hypertensive in the Nord-Trondelag Health Study (HUNT) in Norway (27) 11.5% was reported from the Prevention of Renal Vascular End Disease (PREVEND) study in The Netherlands (28) and 13.0% was reported from the microalbuminuria.

A Genoa Investigation on Complications (MAGIC) study in Italy (20). Differences in the occurrence of microalbuminuria are, therefore, attributable to differing patient characteristics, urine sample collection and the types of tests used.

According to the recently modified renal disease guidelines (Kidney Disease outcome Quality Initiative [K/DOQI]/Kidney Disease: Improving Global Outcomes [KDIGO]) (29), it is advisable to measure urinary albumin since it enhances cardiovascular risk among microalbuminuria positive individuals. Similarly, the 2003 European

Table 4. Clinical and biochemical characteristics of all albuminuria groups in eGFR < 60 ml/min/1.73m^2 vs. eGFR > 60 ml/min/1.73m^2

	Normo albuminuria in eGFR< 60 ml/ min/1.73m^2	Normo albuminuria in eGFR > 60 ml/ min/1.73m^2	P Value	Micro albuminuria in eGFR< 60 ml/ min/1.73m^2	Micro albuminuria in eGFR > 60 ml/ min/1.73m^2	P Value	Macro albuminuria in eGFR< 60 ml/ min/1.73m^2	Macro albuminuria in eGFR > 60 ml/ min/1.73m^2	P Value
Number of patients	87	55		41	33		20	5	
Age (years)	49±11	43±11*	0.002	52±11	48±12	0.14	54±11	47±11	0.25
Males	50 (57%)	45 (82%)	1.00	16 (39%)	26 (79%)*	0.001	7 (35%)	4 (80%)*	0.03
Females	37 (43%)	10 (18%)	1.00	25 (61%)	7 (21%)*	0.001	13 (65%)	1 (20%)*	0.03
BMI Kg/m^2	26±5	28±4*	0.013	28±4	28±5	1.00	28±6	28±5	1.00
MAP (mmHg)	104±13	105±9	0.58	104±12	107±15	0.35	111±18	106±13	0.50
Antihypertensive	1.3±0.4	1.3±0.5	1.00	2.2±0.4	2.4±0.5	0.067	3.4±0.4	3.6±0.5	0.44
CCB	40 (46%)	36 (65%)*	0.026	28 (68%)	27 (82%)	0.28	16 (80%)	5 (100%)	0.54
ACEI	25 (29%)	21 (38%)	0.27	27 (66%)	20 (61%)	0.82	13 (65%)	2 (40%)	0.35
Diuretics	5 (6%)	3 (5%)	0.94	17 (41%)	13 (39%)	1.00	11(55%)	3 (60%)	0.83
α blockers	3 (3%)	2 (4%)	0.95	2 (5%)	--	--	9 (45%)	1 (20%)	0.23
ARBs	15 (17%)	4 (7%)	0.06	4 (10%)	2 (6%)	0.55	2 (10%)	2 (40%)	0.16
β blockers	21 (24%)	8 (15%)	0.28	12 (29%)	16 (48%)	1.00	13 (65%)	4 (80%)	1.00
Statin use	38 (44%)	20 (36%)	0.48	18 (44%)	10 (36%)	0.33	10 (50%)	2 (40%)	1.00
Serum Albumin (g/dl)	3.5±0.4	5±3*	0.001	3.5±0.3	4±2	0.16	3.2±0.5	3.5±0.2	0.051
Hemoglobin (g/dl)	13±2	14±1*	0.001	14±2	14±1	1.00	14±1	14±3	1.00
Hematocrit (%)	39±5	41±4*	0.01	40±5	42±3*	0.03	42±4	41±7	0.77
Cholesterol (mg/dl)	203±51	196±30	0.30	226±45	198±33*	0.003	230±43	231±32	0.95
History of HTN (month)	47±13	24±8*	0.001	125±14	84±10*	0.001	203±21	150±17*	0.001

* $p<0.05$

MAP, Mean arterial blood pressure ; **CCB,** Calcium channels blockers; **ACEi,** Angiotensin converting enzyme inhibitors; **ARBs,** Angiotensin receptor blockers; **HTN,** hypertension ; **eGFR,** estimated glomerular filtration rate.

Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines incorporated screening for microalbuminuria as a recommended test for risk stratification, which helps to determine drug treatment initiation and targeted follow-up (30). However, measurement of microalbuminuria in hypertensive patients was just an optional test in the JNC 7 Guidelines (13). But in the current study it is advisable to measure albuminuria as a marker for early renal impairment in essential hypertensive patients.

Variations in the prevalence of microalbuminuria between the current study and that reported in other studies are mostly due to differences in the selection criteria, and to the techniques used for the detection of microalbuminuria. Another clinical trial that involved patients with mild and moderate essential hypertension showed a 6.1% prevalence of Microalbuminuria (31), this is a considerably lower value than the current study.

These discrepancies are most likely due to different criteria in patient selection i.e. the severity, duration of hypertension, age, race, and the techniques used for the detection of albuminuria. Agewall et al (32) reported a 23% prevalence of microalbuminuria in a population of hypertensive patients who were selected as at high risk for cardiovascular disease. In the current study, we exclude patients who were, diabetic, or had a history or signs of primary renal disease.

Damsgaard et al (33) reported a relatively high prevalence of microalbuminuria in a group of 216 elderly hypertensive patients, Bigazzi and Bianchi (34) reported a high prevalence of microalbuminuria (40%) in a group of 123 unselected patients with essential hypertension. These results are in agreement with the results of the current study.

Conclusions

Albuminuria is a risk marker for prediction of the progression of nephropathy and may reflect hypertensive injury to the kidney so it should be assessed regularly to monitor the impact of antihypertensive therapy. Long-term prospective studies are needed to establish the importance of albuminuria as a predictor of renal morbidity and mortality.

Conflict of Interest

None declared.

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