Microalbuminuria is a late event in patients with hypertension: Do we need a lower threshold?

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Background: Microalbuminuria (MA) is a marker of vascular damage. However, many studies have observed an increased risk at lower levels of albuminuria than are currently used to define MA.

Aim: To verify early cardiovascular changes occurring before MA in hypertensive patients.

Materials and methods: One hundred and fifty hypertensive patients and 60 normotensive individuals were divided into normotensive individuals with normal left ventricular (LV) geometry (Group I), hypertensive patients with normal LV geometry (Group II), and hypertensive patients with abnormal LV geometry (Group III). The LV mass index, ambulatory arterial stiffness index, flow-mediated dilatation of the brachial artery, and intima-media thickness (IMT) of the common carotid were assessed. Urinary albumin/creatinine ratio was determined using a morning spot-urine sample.

Results: Compared with Group I, ambulatory arterial stiffness index and IMT were significantly increased and flow-mediated dilatation was significantly decreased in Group II; however, MA did not differ between both groups. These changes were augmented when Group III was compared with Group II. MA significantly increased in Group III compared with Group II. Receiver operating characteristic analysis revealed that MA, with a cut-off value of 19.25 mg/g, predicted increased IMT, and abnormal LV geometry in a statistically significant manner.

Conclusion: Many vascular changes, in the form of increased IMT, reduced vasodilator capacity, and increased arterial stiffness, preceded MA and any change in LV geometry. The results presented here strengthen the usefulness of adopting a lower cut-off to define MA.

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Introduction

Microalbuminuria (MA) is known to be associated with atherosclerosis and is a strong independent predictor of an increased risk of cardiovascular morbidity and mortality independent of traditional risk factors [1,2]. MA is a well-known marker of underlying vascular dysfunction and has been correlated with the structural and functional integrity of the vasculature [3].

The prevalence of MA is low in the absence of cardiovascular risk factors and progressively increases with the number of cardiovascular risk factors. The main correlate of MA is blood pressure, either systolic or diastolic [4]. The relationship between blood pressure and MA is continuous and graded because the prevalence of MA increases with the severity of hypertension [5].

However, some studies have found that increased risk is observed at much lower levels of MA than are currently used to define MA [6].

Methods

This study was carried out in the Cardiology Department at El Minya University Hospital, Minya, Egypt, over a 13-month period between December 2013 and January 2015.

This study included 150 newly discovered untreated hypertensive patients (diagnosed according to European Society of Hypertension/European Society of Cardiology guidelines for management of arterial hypertension) compared with 60 sex and age matched healthy controls [7]. They were classified into the following three groups: Group 1: 60 normotensive apparently healthy individuals with normal (left ventricular) LV geometry; Group 2: 54 hypertensive patients with normal LV geometry; and Group 3: 96 hypertensive patients with abnormal LV geometry.

The following exclusion criteria were used in this study: (1) tobacco smoking; (2) previous myocardial infarction (3) coronary bypass graft; (4) cardiac valve disease; (5) stroke; (6) diabetes; (7) dyslipidaemia; and (8) obesity.

All of the participants (after written consent) were subjected to the following measurements: history taking, clinical examination, office blood pressure measurement (patients with a systolic blood pressure ⩾140 mmHg and diastolic blood pressure ⩾90 mmHg were considered to be hypertensive), body mass index and body surface area measurements, laboratory investigation (fasting and postprandial blood sugar, lipid profile, blood urea nitrogen, serum creatinine, glomerular

Abbreviations	
MA	microalbuminuria
IMT	intima-media thickness
AASI	ambulatory arterial stiffness index
ACR	albumin-to-creatinine ratio
FMD	flow-mediated vasodilatation
GTN-MD	glyceryl trinitrate-mediated dilatation

filtration rate, and quantification of albumin in urine), and ambulatory blood pressure monitoring using AMP50 (China).

Calculation of the ambulatory arterial stiffness index

For each participant, the regression slope of diastolic on systolic blood pressure was calculated from 24-hour recordings. The regression line was not forced through the origin (intercept 0) because blood pressure does not drop to 0 when the flow drops to 0 during diastole [8].

The rationale underlying this is that for any given increase in distending arterial pressure, systolic and diastolic pressures tend to increase in a parallel fashion in a compliant artery. By comparison, in a stiff artery, the increase in systolic pressure is accompanied by a lesser increase, or even by a decrease in diastolic pressure.

The ambulatory arterial stiffness index (AASI) was defined as 1 minus the regression slope. The stiffer the arterial tree, the closer the regression slope and AASI are to 0 and 1, respectively [8].

Assessment of MA

Urinary albumin and creatinine concentrations were determined using a morning spot-urine sample. Urine albumin was determined using the enzyme-linked immunosorbent assay method [disease related group microalbumin enzyme-linked immunosorbent assay (EIA-2361) USA], whereas urinary creatinine was assessed with the kinetic Jaffe' method using the Autoanalyzer Modular (Hitachi–Roche Diagnostics, Manneheim, Germany). The urinary albumin-to-creatinine ratio (ACR) was then calculated. MA was defined as an ACR of 30–300 mg/g in two positive tests from three [9].

Colored duplex ultrasound to measure the intima-media thickness

A carotid ultrasound evaluation was conducted on all of the participants in this study to determine the intima-media thickness (IMT) and to detect carotid plaques using the high-resolution B-

mode ultrasound equipment Medison 9900 Multi-beam 30 UL (Korea) equipped with a liner probe (7.5 MHz) and a standardized protocol [10].

The individuals were investigated in the supine position, and the IMT of the far wall was evaluated as the distance between the luminal–intimal interfaces and the medial–adventitial interface approximately 1.5 cm proximal to the carotid bifurcation. The IMT measurements were obtained from four contiguous sites at 2-mm intervals, and the average was calculated. The mean IMT (the mean of both right and left side) was assessed. Simultaneously, the maximum IMT (the highest value either right or left) was also assessed. The IMT is considered to be abnormal at levels >0.072 cm [11].

Plaques were defined as focal widenings relative to adjacent segments with protrusions into the lumen of calcified or noncalcified material [12].

Colored duplex ultrasound to test endothelial functions

Colored duplex ultrasound was conducted on all of the participants. The mean right brachial artery antero–posterior diameter was measured 3–5 cm above the elbow between the media and adventitia from four cycles synchronized with the end diastole at the R-wave peaks [13].

A basic scan of the flow was taken. Then, a 2nd scan was taken after applying a pneumatic tourniquet of 250–300 mmHg (using mercurial sphygmomanometer) for approximately 4.5 seconds. The scan was taken 60 seconds after releasing the tourniquet measuring the maximum flow-mediated vasodilatation (FMD). A 3rd scan was

measured after 15 minutes of rest to allow for the recovery of the artery after FMD, which was the basis of the glyceryl trinitrate-mediated dilatation (GTN-MD) reading. A 4th scan was taken 4 minutes after sublingual administration of 400 μg of GTN spray.

The FMD percentage was calculated using the following equation:

$$FMD\% = \frac{2^{nd}\ Scan - 1^{st}\ scan}{1^{st}\ scan} \times 100 \qquad (1)$$

The GTN-MD percentage was calculated using the following equation:

$$GTN\text{-}MD\% = \frac{4^{th}\ Scan - 3^{rd}\ scan}{3^{rd}\ scan} \times 100 \qquad (2)$$

The dilatation percentage was calculated using the following equation:

$$DilRatio = \frac{FMD\%}{GTN\text{-}MD\%} \times 100 \qquad (3)$$

Echocardiography evaluation of the LV mass index (MI) was performed. An evaluation was conducted according to the following equation:

$$LV\ mass\ (g) = 0.8\{1.04[(LVIDD + PWTD + IVSTD)3 \\ - (LVIDD)3]\} + 0.6\ g \qquad (4)$$

where IVSTD = interventricular septum thickness in diastole; LVIDD = left ventricular internal diameter in diastole; and PWTD = posterior wall thickness in diastole. LV mass was then indexed to body size by dividing the raw LV mass by height raised to the power of 2.7.

LV hypertrophy (LVH) was defined as LVMI > 51 gm/ht$^{2.7}$ [14]. The geometric pattern was determined by calculating the relative wall thickness (RWT) as follows:

Table 1. Comparison of age between in the study groups.

	Group 1 (n = 60)		Group 2 (n = 54)		Group 3 (n = 96)		p	
	Mean	SD	Mean	SD	Mean	SD	G1 vs. G2	G2 vs. G3
Age (y)	45.25	7.88	47.39	8.22	48.78	5.19	0.419	0.466

G = group; SD = standard deviation.

Table 2. Comparison of the blood pressure data and the ambulatory arterial stiffness index in between the study groups.

	Group 1 (n = 60)		Group 2 (n = 54)		Group 3 (n = 96)		p	
	Mean	SD	Mean	SD	Mean	SD	G1 vs. G2	G2 vs. G3
Office SBP	127.35	5.32	165.56	19.31	170.72	13.68	<0.001	0.276
Office DBP	77.50	6.39	97.78	10.03	97.67	11.57	<0.001	0.970
Mean 24 h SBP	123.05	6.65	152.11	22.36	148.59	9.09	<0.001	0.436
Mean 24 h DBP	74.8	6.63	94.33	10.63	92.03	7.1	<0.001	0.364
AASI	0.52	.062	0.73	0.104	0.79	0.08	<0.001	0.011

DBP = diastolic blood pressure; G = group; Mean 24 h DBP = mean 24-hour diastolic blood pressure; Mean 24 h SBP = mean 24-hour systolic blood pressure; SBP = systolic blood pressure; SD = standard deviation.

$$RWT = 2 \times PWTD/LVIDD \text{ [14]} \tag{5}$$

The following four distinct geometric patterns were described [14]: normal geometry (normal LVMI with a RWT < 0.45), concentric remodeling (normal LVMI with a RWT > 0.45), concentric hypertrophy (increased LVMI with RWT > 0.45), and eccentric hypertrophy (increased LVMI associated with RWT < 0.45).

Statistical analysis

The data were analyzed using SPSS (SPSS Inc., Chicago, Il, USA), version 16 for Windows. All of the data were reported as the mean ± standard deviation. Student t test was used to compare the means of the two groups. The Mann–Whitney U test was used to compare nonparametric variables. Differences were considered to be significant at a two-tailed $p \leqslant 0.05$. Receiver-operating characteristics curve analysis was performed to assess the accuracy of MA at detecting increased IMT and LV geometry.

Results

As shown in Table 1, the study groups were all age-matched. There was a statistically significant difference between Group 1 and Group 2 in the
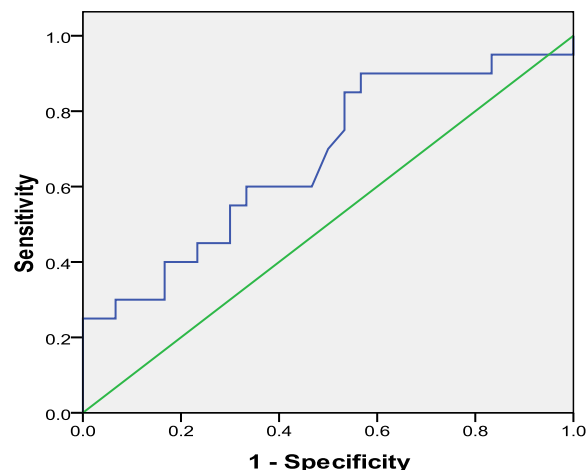

Fig. 1. *Receiver operating characteristic analysis for the prediction of increased intima-media thickness.*

office-based and 24-hour mean systolic and diastolic blood pressures, while there was no significant difference between Group 2 and Group 3 in these parameters. Meanwhile, there were significant differences in the AASI between Group 1 and Group 2 and Group 2 and Group 3 (Table 2).

The carotid IMT significantly increased in Group 2 compared with Group 1; the carotid

Table 3. *Comparison of the intima-media thickness and flow-mediated vasodilatation between the study groups.*

	Group 1 (*n* = 60)		Group 2 (*n* = 54)		Group 3 (*n* = 96)		*p*	
	Mean	SD	Mean	SD	Mean	SD	G1 vs. G2	G2 vs. G3
RCCA-IMT	0.055	0.006	0.083	0.043	0.089	0.027	0.007	0.535
LCCA-IMT	0.058	0.011	0.078	0.024	0.109	0.048	0.002	0.013
MCCA-IMT	0.058	0.008	0.083	0.030	0.102	0.033	0.001	0.047
FMD%	16.08	6.483	10.10	11.01	6.13	4.2	0.046	0.073
Dilatation ratio	94.8	40.06	50.28	26.03	54.05	30.4	<0.001	0.660

FMD% = flow mediated dilatation percent; G = group; LCCA = left common carotid; MCCA = mean common carotid artery; RCCA = right common carotid artery; SD = standard deviation.

Table 4. *Comparison of albuminuria between the study groups.*

	Group 1 (*n* = 60)		Group 2 (*n* = 54)		Group 3 (*n* = 96)		*p*	
	Mean	SD	Mean	SD	Mean	SD	G1 vs. G2	G2 vs. G3
Albuminuria (UACR) in mg/g	8.25	2.544	16.65	21.49	46.74	49.63	0.09	0.019

UACR = urinary albumin creatinine ratio.

Table 5. *Receiver operating characteristic analysis for the prediction of an increased intima-media thickness.*

	Increased IMT (⩾0.072 cm)				Abnormal LV geometry			
	AUC	Cut-off value	Sensitivity	Specificity	AUC	Cut-off value	Sensitivity	Specificity
MA	0.674	19.25	60	66	0.766	19.250	.625	88

AUC = area under the curve; IMT = intima-media thickness; LV = left ventricular; MA = microalbuminuria.

IMT increased further in Group 3 compared with Group 2 (Table 3).

There was a significant decrease in the FMD and the dilatation ratio in Group 2 compared with Group 1, while the FMD tended to decrease significantly in Group 3 compared with Group 2 (Table 3).

However, albuminuria only significantly differed between Group 2 and Group 3 (i.e., hypertensive patients with and without LVH) because albuminuria was significantly higher in Group 3 versus Group 2 but not between normotensive patients (Group 1) and hypertensive patients without LVH (Group 2; Table 4).

Finally, receiver-operating characteristics analysis revealed that a MA level of 19.25 mg/g accurately and significantly predicted an increased IMT level ($\geqslant$0.072 cm) and abnormal LV geometry (Table 5; Figs. 1 and 2).

Discussion

MA is a biomarker for chronic kidney disease and an independent predictor of cardiovascular and all-cause mortality [15]. Furthermore, MA is associated with a four-fold increased risk of ischemic heart disease in patients with untreated hypertension or borderline hypertension [16].

The main finding from this study was that vascular changes (IMT, FMD, and AASI) significantly differed between the study groups (lowest in Group I and highest in Group 3). Similarly, the blood pressure significantly differed between these groups (lowest in Group 1 and highest in Group 3). Thus, vascular changes are assumed to

Fig. 2. *Receiver operating characteristic analysis for the prediction of abnormal left ventricular geometry.*

increase during the progression of hypertensive disease.

However, albuminuria significantly differed only between Group 2 and Group 3 (i.e., hypertensive patients with and without left ventricular hypertrophy) but not between normotensive patients (Group 1) and hypertensive patients without LVH (Group 2).

Despite the importance of MA as a marker of high risk, these findings indicate that it is a relatively late LVH event (one area of subclinical target organ damage); many other sensitive markers occurred earlier. Therefore, these results suggest that albuminuria is a late rather than early marker of end organ damage.

From a pathophysiological point of view, this finding seems reasonable because MA reflects vascular (renal) damage; thus, risk might be increased at very low levels of urine albumin.

These results agree with many other studies [6,15,17] that have found an increased risk at much lower levels of albuminuria than currently used to define MA. Such low levels were shown to predict heart disease, hypertension, and death, independent of age, sex, renal function, diabetes, and lipids in patients with cardiovascular disease and hypertension as well as in the general population. Furthermore, in 2010, Cerasola et al. [18] found clear evidence that urinary albumin excretion levels, even below the cut-off values currently used to diagnose MA, are associated with an increased risk of cardiovascular events.

Moreover, in a community-based sample of middle-aged nonhypertensive, nondiabetic individuals, low levels of urinary albumin excretion well below the current MA threshold predicted cardiovascular disease development [19]. These observations add to the growing body of evidence that challenges the notion that urine ACR < 30 mg/g indicates "normal" albumin excretion [19].

Moreover, results from The Third Copenhagen City Heart Study have shown that even lower levels of albuminuria (5 µg/min) are associated with a worse risk profile and have a strong independent prognostic value in hypertensive patients [20].

Similarly, Ratto et al. [21] demonstrated that lowering the ACR threshold (11.5 mg/g) that is currently used to detect MA might improve cost-effectiveness in identifying patients with LVH as the sensitivity and specificity of this adopted threshold in identifying patients with LVH was 39% and 92%, respectively [21]. Another study also detected that low-grade albuminuria was
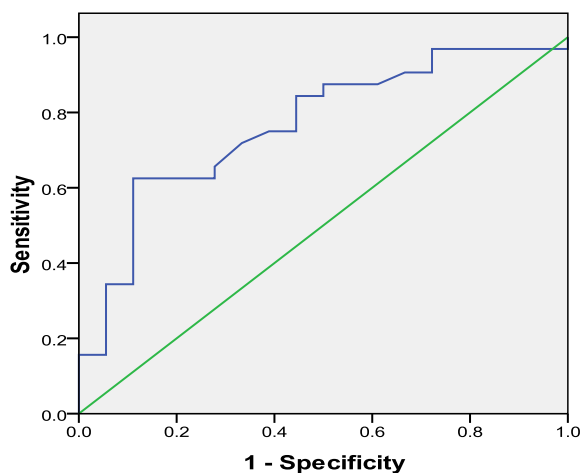
associated with LV dysfunction in the general population. Thus, the conventional urinary ACR-threshold of MA (30 mg/g) may be too conservative given that end-organ damage, such as LVH, is observed with increased frequency at much lower levels [22].

This relatively late occurrence of MA in hypertensive patients may be explained by the challenges of different albumin detection techniques. The nature of urinary albumin is now known to be complex. Indeed, albumin is excreted as a mixture of intact albumin (immunoreactive) detected by routine tests, albumin-derived peptides that are not detected by routine antibody-based tests, and a species of intact albumin (immuno-unreactive albumin), also not detectable with antibody-based tests [9].

The urine albumin concentration has traditionally been measured with quantitative immuno-chemical methods, such as immunonephelometry, immunoturbidimetry, and radioimmunoassay [9]. High performance liquid chromatography techniques used to measure urinary albumin indeed found some urinary albumin molecules that are not detected with the standard antibody techniques.

Moreover, a new test based on high performance liquid chromatography identifies the entire immune-reactive and immuno-unreactive intact albumin (total intact albumin) in the urine [13]. An underestimation of the total intact urinary albumin with conventional methods is especially relevant for a low albumin execration rate (<20 μg/min by current methods) [9].

Study limitations

Spot urine sampling is subject to both incidental diurnal variation and the prevalent concentration/dilution of the urine sample, which over- and underestimates true albumin excretion, respectively. To overcome this, the urinary albumin/creatinine ratio is used. However, this measurement is also complicated by the fact that creatinine excretion varies between sex and within sex.

Conclusion

Because albuminuria only significantly differed between the hypertensive patients with and without LVH, it is tempting to speculate that MA is a marker of end-organ damage that occurs relatively late in the course of hypertension. MA showed to be a useful tool in the complex process of risk stratification revealing a great specificity and even a lower sensibility. MA might, at least,

reflect renal-vascular damage, while FMD, arterial stiffness, and IMT might be parameters of vascular stress and/or injury that precede end-organ damage.

The need to limit costs without compromising the accuracy of the diagnostic process is rapidly becoming a major issue for public health. Thus, we need to devise new, accurate, easy-to-use, and inexpensive ways to identify patients at risk. The results presented here strengthen the usefulness of adopting a lower cut-off to define MA.

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