

Intensive treatment of persistent microalbuminuria: determinants of treatment resistance

Research Article

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Abstract: Aims. Persistent microalbuminuria after treatment is a common finding. This study tried to evaluate the causes of treatment resistance. Patients and methods. Sample: 204 patients treated with renina-angiotensin-axis (RAA) blocking drugs that showed positive microalbuminuria. Treatment was increased during three months to reach a BP < 130/80 mmHg and to obtain maximal RAA blockade. Then patient were classified as normoalbuminuric after treatment (N group) and microalbuminuric in spite of treatment (M). Results. Mean microalbuminuria at recruitment was 48.5 ± 25.6 mg/24h in N group and 90.0 ± 140.3 mg/24h in M group. It was reduced to 16.1 ± 10.0 mg/day in N group and to 83.5 ± 138.2 mg/day in M group. At start, mean SBP and mean DBP were not different between groups. After treatment SBP and DBP pressure were reduced in both groups (differences between groups were not significant). Combined control of BP showed a slight increase in the two groups but it have only statistical significance in the N group ($p = 0.031$, McNemar test). Conclusions: Persistent microalbuminuria seems to be associated to poor blood pressure control. Effective blood pressure reduction was followed by urinary albumin excretion decrease. Baseline severity of microalbuminuria was the only clear predictor of remission after treatment.

Keywords: Microalbuminuria • Hypertension • Remission • Response to treatment

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1. Introduction

Increased urinary albumin excretion (UAE) –the so called microalbuminuria– has been recognized in diabetic patients not only as a predictor of progression to diabetic renal disease but also as a powerful independent cardiovascular risk marker [1-3]. Also in

non diabetic hypertensive patients high UAE has been shown to predict cardiovascular events: A continuous relation between UAE and cardiovascular, as well as non-cardiovascular, mortality has been found in the general population [4-8]. Thus, the prevention of elevated UAE is an important therapeutic target for the prevention of renal and cardiovascular events. In the same way it is

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very important to explore the modifiable factors whose treatment might reduce microalbuminuria [9,10].

Intervention studies with ACE inhibitors (ACEI) or angiotensin II type 1 receptor blockers (ARB) in subjects with type 2 diabetes have shown that reduction of microalbuminuria can be induced [11–13]. Moreover, it has been reported that regression of microalbuminuria in type 1 diabetes occurred more frequently than progression to persistent proteinuria when adequate treatment is provided [14]. Nevertheless, a substantial proportion of diabetic and/or hypertensive patients still show microalbuminuria in spite of being treated with renin-angiotensin axis blocking drugs [15].

In a previous report we have described the possible causes of resistant microalbuminuria and the results of intensive treatment [16]. This report describes the characteristics of patients who became normoalbuminuric compared to those who remained microalbuminuric after modifying treatment.

2. Patients and methods

The sample was recruited among diabetic and hypertensive patients attended in primary care settings. Criteria for diagnosis have been published elsewhere [16]. An initial measurement of albumin excretion ratio by stick (MICROALBUSTIX®, Bayer AG, Leverkusen, Germany) was performed and, when it rendered positive, the measurements of UAE was reassured in 24-h urine collections. Microalbuminuria was defined as an of 30–299 mg/day in a 24-h urine collection (equivalent to 30–299 mg/g creatinine in a random spot sample). Those patients taking ARB or ACEI for at least six months before starting the study who presented confirmed microalbuminuria in 24-h urine collection were enrolled. Among 204 participants, mean age was 65.1 ± 11.5 years, 56.4% were male, and 95.1% were hypertensive. They were 92 patients who became normoalbuminuric (N group) and 112 subjects remained microalbuminuric after treatment (M group). Baseline demographic and clinical characteristics of each group are described in Table 1.

Each subject underwent standardized physical examination, biochemical measurements under fasting condition, and measurement of urinary albumin excretion in a 24-h urine collection. Glomerular filtration rate (GFR) was estimated using the abbreviated MDRD formulation. Treatment was recorded (ACEI or ARB, other classes of antihypertensive, lipid lowering or antidiabetic drugs; as well as dosage and time of administration of each drug).

	Normoalbuminuric	Microalbuminuric	Units
n	92	112	
Age	65.4 ± 11.1	65.0 ± 11.9	Years
Gender	56.6/43.4	60.7/39.3	%Male/ Female
Waist perimeter	100.5 ± 10.7	100.4 ± 17.0	Cm
Body mass index	31.4 ± 4.1	31.9 ± 6.3	Kg/m ²
Diabetic	51.1	50.8	%
Abdominal obesity	44.6	50.0	%

Table 1. Comparative data at baseline. Differences are not significant.

Afterwards, treatment was intensified in order to reach the straight objectives suggested by the standard strategies for diabetes mellitus, hypertension, and hyperlipidemia from the clinical practice recommendations of the 2007 Clinical Guidelines for the Management of Hypertension of the European Cardiology and Hypertension Societies [17] (blood pressure <130/80 mmHg) and the 2007 American Diabetes Association guidelines for diabetes mellitus (as follows: HbA1C <7.0%; and lipid profile <200 mg/dl for total cholesterol, <150 mg/dl for triglyceride, and >40 mg/dl for HDL). The follow-up period was three months [18]. Remission of microalbuminuria was defined as shift of urinary albumin excretion from microalbuminuria to normoalbuminuria (<30 mg/24h). Therapeutic changes included: 1) Adding antihypertensive agents –different from RAA blocking drugs; 2) Modify pills intake schedule either splitting the dosage or adding a nighttime dose; 3) Change for an ACEI or ARB with long-lasting activity –i.e. enalapril to telmisartan; 4) Increase ACEI or ARB dosage up to maximal recommended one.

The study protocol and informed consent procedure were approved by the Ethics Committee of the Hospital Infanta Cristina, Badajoz.

Results are expressed as mean $\pm$ 1 standard deviation or as median (interquartile range) whenever the sample did not follow a normal distribution. Kolmogorov–Lilliefors Test showed that urinary albumin excretion did not follow a normal distribution so these values were compared using Wilcoxon test for paired data. Other continuous values were compared through paired Student “t” test. The Square Chi test (with Yates correction if needed) was used for discrete data comparison. The McNemar test was used for comparison of discrete data changes. All statistical tests were two-sided. P values

lower than 0.05 were considered as significant. Analysis was developed with the statistical package PASW 17.0.

3. Results

Mean SBP and mean DBP were not different between groups (see Table 2). For a target BP < 130/80 mmHg the percentage of controlled patient was low, although it was slightly better in N group this difference was not statistically significant. All results are shown in Table 2. The number of patients taking two or more antihypertensive drugs was very similar: 57.2% in the N group and 48.7% in the M group were treated with ($p = 0.221$). Number of drugs used in each group is shown in Figure 1.

Mean microalbuminuria at recruitment was 40.0 (33.9-54.3) mg/24h in N group and 59.0 (40.9-93.2) mg/24h in M group ($p < 0.001$, Wilcoxon unpaired test). Mean microalbuminuria was reduced to 16.7 (6.5-25.0) mg/day in N group ($p < 0.001$ vs baseline, Wilcoxon paired test). Mean 24h albumin excretion decrease also

in M group to 50.0 (34.8-76.9) mg/day ($p < 0.001$ vs baseline). Differences between groups were still significant when the study ended ($p < 0.001$). In group M 17 patients showed an increment of microalbuminuria; contrariwise, 12 patients get a reduction deeper than 32 mg.

After treatment SBP pressure was reduced in both groups (N $p < 0.001$, M $p < 0.001$; Student t test; differences between groups were not significant). DBP decreased in a similar way in N group subjects ($p = 0.015$) and M group ones ($p = 0.002$), without differences between groups. Combined control of BP showed a slight increase in the two groups but it only had statistical significance in the N group ($p = 0.031$). No changes in SBP control were detected in N group nor in M group. Those patients who became normoalbuminuric got a better control of DBP, but the percentage of subjects with controlled DBP did not change in the M group. All values are shown in Table 3. Figure 2 show BP and

	Normoalbuminuric	Microalbuminuric	Units
SBP	139.3±13.9	142.6±17.3	mmHg
DBP	79.8±10.4	81.7±11.5	mmHg
Pulse pressure	59.5±12.8	60.9±15.3	mmHg
HR	72.9±9.3*	75.4±8.3	bpm
SBP CONTROL	20.7 (10.5-30.9)	18.8 (11.6-26.0)	% (95% CI)
DBP CONTROL	41.3 (31.1-51.5)	33.9 (25.1-42.7)	% (95% CI)
GLOBAL BP CONTROL	15.2 (5.0-25.4)	13.4 (7.1-19.7)	% (95% CI)

* $p = 0.049$ vs. baseline (Student t test). Other differences between groups are not significant. SBP, systolic blood pressure. DBP, diastolic blood pressure. HR Heart rate. BP Blood pressure.

Table 2. Blood pressure before treatment

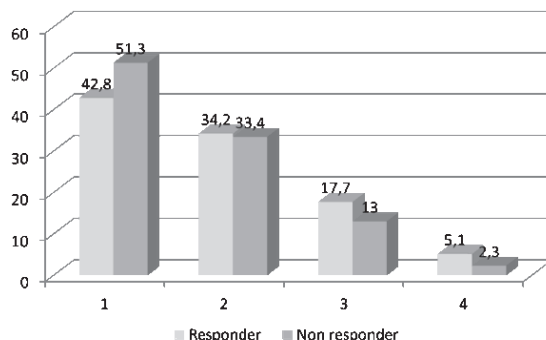


Figure 1. Number of antihypertensive drugs used. Differences between groups are not significant.

	Normoalbuminuric	Microalbuminuric	Units
SBP	136.9±12.6	136.8±14.6	mmHg
DBP	79.2±12.6	79.3±14.6	mmHg
Pulse pressure	56.7±9.0	57.3±16.0	mmHg
HR	72.9±9.4	75.2±8.4	bpm
SBP CONTROL	23.9 (13.7-34.1)	24.1 (16.2-32.0)	% (95% CI)
DBP CONTROL	48.9 (38.7-59.1)*	41.1 (32.0-50.2)	% (95% CI)
GLOBAL BP CONTROL	18.5 (8.3-28.7)**	16.1 (9.3-22.9)	% (95% CI)

* $p = 0.036$ vs. baseline (McNemar test). ** $p = 0.031$ vs. baseline (McNemar test). Differences between groups are not significant. SBP, systolic blood pressure. DBP, diastolic blood pressure. HR Heart rate. BP Blood pressure.

Table 3. Blood pressure after treatment

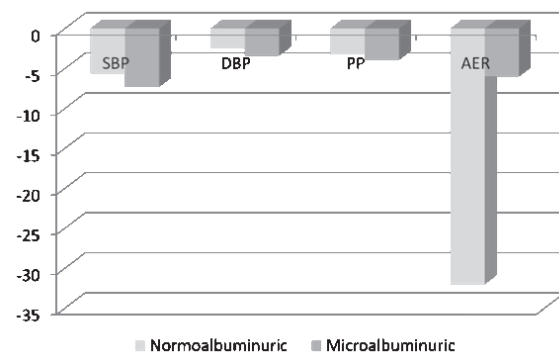


Figure 2. Mean blood pressure (mmHg) and urinary albumin excretion (UAE, mg/24h) reductions. Changes in BP are not significant. UAE decreased more in normoalbuminuric group ($p < 0.001$, Wilcoxon test).

albumin excretion reduction in each group. The non hypertensive patients showed a decrease of SBP from 131.8 ± 19.0 to 125.3 ± 14.3 mmHg (difference is not significant). DBP decreased from 79.0 ± 3.5 to 77.7 ± 7.4 mmHg (without statistical signification). No cases of symptomatic hypotension were reported.

Other biochemical values at baseline have been showed in Table 4. There were not statistical differences between responder subjects and non responder ones. Although serum creatinine after treatment was lower in N group (0.86 ± 0.21 mg/dl) than in M group (0.96 ± 0.30 mg/dl, $p = 0.009$), no changes in GFR were detected (N group 91.5 ± 34.7 ; M group 84.1 ± 38.4 ml/min; difference between groups was not significant).

No differences were found in the prevalence of patients who did not reach full dosage of RAA blockers as suggested by the VII Report of the National Joint Committee [19]. When the once daily use of short-life drugs was evaluated (such are captopril, enalapril or losartan) the results were very similar in both groups. The same number of patients was taken pills at night. Taken all these possible problems into account 44.4% of M patients and 46.8% of N group were not receiving adequate treatment (without statistical signification). All values are shown in the Figure 3.

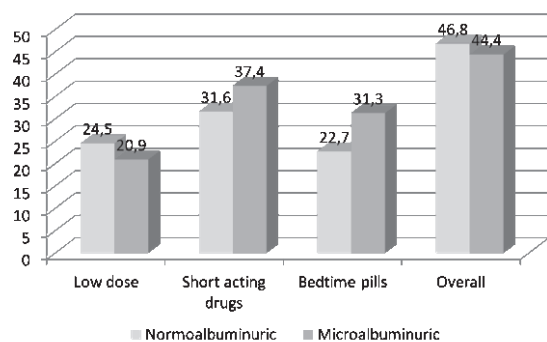


Figure 3. Possible therapeutic mistakes. Differences between groups are not significant.

4. Discussion

A reduction of urinary albumin excretion intensity was seen in both groups. Achievement of remission after increased treatment of microalbuminuria was only related to baseline microalbuminuria. A better control of DBP was also seen in those patients who achieve remission. No differences were found in baseline characteristics of the subjects. Therapeutic schedule previously used was not different between groups.

Alterations in the fraction of plasma filtered by the glomerulus due to changes in blood pressure and intra-glomerular pressure regulation result in relatively large changes in urinary albumin excretion. It is therefore not surprising that several studies have shown a positive correlation between micro-albuminuria and blood pressure, especially at pressures $<150/90$ mmHg [20,21]. Notwithstanding, the lack of relationship between changes in BP and urinary albumin excretion in our study suggests that the differences in microalbuminuria reduction between treatment groups were not only related to differences in BP reduction. Thus, other factors not related to blood pressure might be involved. The intimate relationship between low-level albumin excretion and vascular permeability makes UAE highly sensitive to the presence of any inflammatory process, including cardiovascular disease. In this regard, the kidney is ideally placed to amplify any small changes in systemic vascular permeability [22]. Moreover, glomerular permeability to albumin is dependent on membrane charge selectivity as well as size selectivity. The negative charge conferred on the glomerular membrane by its constituent glycoproteins plays a role in restricting the permeability of anionic proteins. Loss of glomerular charge selectivity has been found in both diabetic and non-diabetic populations with microalbuminuria [23,24]. Genes also may play a major role in many processes related to diabetic complications and there are numerous

	Normoalbuminuric		Microalbuminuric	
	BASAL	FINAL	BASAL	FINAL
Creatinine	0.87 ± 0.24	0.86 ± 0.21	0.94 ± 0.29	0.96 ± 0.30
Urate	5.8 ± 1.5	5.9 ± 2.0	6.1 ± 1.6	6.0 ± 1.9
Total cholesterol	199.4 ± 33.1	196.3 ± 33.1	197.4 ± 36.8	194.5 ± 30.1
HDL	52.5 ± 13.4	52.8 ± 12.2	53.1 ± 12.1	54.0 ± 15.0
LDL	119.7 ± 27.9	116.9 ± 25.6	119.1 ± 33.9	117.0 ± 34.7
Triglycerides	129.3 ± 69.7	132.3 ± 70.9	131.3 ± 56.3	129.9 ± 62.1
GFR	89.4 ± 26.1	90.2 ± 28.3	85.6 ± 38.0	85.3 ± 36.4

GFR: Glomerular filtration rate, ml/min/1.73 m² body surface. All other values expressed as mg/dl. Differences between groups are not significant. HDL, high density lipoproteins. LDL, low density lipoproteins.

Table 4. Biochemical parameters

genetic studies on late diabetic complications including diabetic nephropathy and the role of diabetes duration, which is considered to be an important confounder. However, efforts to identify specific genetic patterns have produced very contradictory and disappointing results [25-26].

Another possible explanation for the diverting results may be that the role of diabetes duration before the development of complications [27]; unfortunately this variable was not included in the protocol design. Nevertheless, the age of diabetic included was closely similar in both groups and so, it seems unlikely a significant difference in the evolution time of diabetes mellitus. In the light of these findings severity of microalbuminuria is the most powerful predictor of treatment response and blood pressure is not the definitive cause of the intensity of UAE.

The large number of randomized trials of antihypertensive therapy, both those comparing active treatment versus placebo and those comparing treatment regimens based on different compounds, confirm the conclusion that the main benefits of antihypertensive treatment are due to lowering of blood pressure *per se*, and are largely independent of the drugs employed [28]. In the I-SEARCH study, aimed to define the prevalence of microalbuminuria in hypertensive outpatients attending a cardiologist or internist, it was notable that over three-quarters of the study population had poorly controlled hypertension, even though antihypertensive medications were widely prescribed. Indeed, the vast majority (95%) of patients in the I-SEARCH study were receiving treatment for hypertension [29]. Our results agreed somehow with this view: microalbuminuric patients in spite of RAA blockers treatment showed a poor BP control and the reduction of BP got a significant reduction in the severity microalbuminuria, but clinical remission was obtained only in those patients with lower UAE.

Inhibition of the RAA either with ACE inhibition or ARBs is particularly effective at reducing urinary albumin excretion rates, with the response being greater than that seen with other forms of antihypertensive therapy [30]. RAA blockers, but not other classes of antihypertensive (i.e. diuretics, beta blockers, and classic calcium antagonists) can normalize glomerular capillary hydraulic pressure by efferent glomerular arteriolar vasodilatation. In turn, these changes may inhibit or lessen later development of glomerular sclerosis in experimental kidney disease (i.e., amino nucleoside nephrosis) [31,32]. But the mechanisms whereby ACE inhibitors ameliorate glomerular sclerosis might be beyond the hemodynamic effects: The benefit appears to represent

a combination of short-term hemodynamic effects and potentially the inhibition of a variety of growth factors (i.e. platelet derived growth factor, PGDF) interacting with angiotensin II that can lead to overproduction of proteins and extracellular matrix, as well as mesangial cells hypertrophy [33-35]. Although the dose-response relationship with respect to BP lowering is flat, the increased effectiveness of higher doses of ARB with respect to urinary albumin excretion is clinically relevant. Effects of ARB beyond BP have been more obvious when higher doses were employed; such is the result of IRMA (Irbesartan for Reducing MicroAlbuminuria) trial where only the branch treated with the highest dose of irbesartan showed significant differences versus placebo in microalbuminuria remission [12]. Nevertheless, in comparative terms non responder patients were receiving similar doses of RAA blocking drugs as responder ones; so that, incomplete drugs dosage did not seem to account for the differences between the groups.

The Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study found a striking correlation of urinary albumin excretion and night time SBP measured through ambulatory BP monitoring: the sub-cohort with higher night-time than daytime BP had significantly higher albumin excretion compared with patients with lower night-time than daytime BP [36]. In type 1 and type 2 diabetes, higher night-time SBP predicted the onset of microalbuminuria [37,38]. This situation might have clinical relevance since it has been established that bedtime dosing is more effective than morning dosing to reduce nocturnal BP [39,40]. Again it was not found that administration of antihypertensive drugs at bedtime were different between both groups. A second related parameter is the blood pressure variability. It has recently also been shown to increase cardiovascular events and it is associated to night time changes in blood pressure and the long lasting effect of antihypertensive drugs [41,42]. Nevertheless, any conclusion at this respect has an important limitation since 24h ambulatory blood pressure monitoring was not performed.

Some conclusions can be drawn: 1) Persistent microalbuminuria seems to be associated to poor blood pressure control in both groups and, 2) an effective blood pressure reduction is followed by a decrease in the amount of urinary albumin excretion. Most important, the intensity of microalbuminuria is the only clear predictor of unachieved remission after treatment. It is needed to research more deeply in the pathophysiology of microalbuminuria in order to find more effective treatments for this problem.

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