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The prognostic significance of microalbuminuria in non-diabetic acute stroke patients

Wojciech Turaj, Agnieszka Słowik, Urszula Wyrwicz-Petkow, Joanna Pankiewicz, Tomasz Iskra, Monika Rudzińska, Andrzej Szczudlik

Department of Neurology, Collegium Medicum, Jagiellonian University, Cracow, Poland

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SUMMARY

Background: *Microalbuminuria (MA) is thought to be a marker of widespread vascular damage. It is associated with increased mortality in diabetes mellitus, hypertension and acute myocardial infarction. The aim of the present study was to evaluate the prognostic significance of MA in non-diabetic acute stroke patients.*

Material and methods: *We studied 52 patients (mean age 69.3±12.5 years) diagnosed with ischemic stroke confirmed by computed tomography, who were admitted to the Stroke Unit within 24 hours after the onset of symptoms. The control group consisted of 37 age- and gender-matched subjects (mean age 65.2±5.7 years), examined 3 to 18 months after ischemic stroke. We excluded patients with diabetes mellitus, positive urinalysis, proteinuria, hepatic or renal insufficiency, neoplastic disease or clinical signs of infection. The severity of the neurological deficit was assessed by the Scandinavian Stroke Scale (SSS). The albumin excretion rate was measured in daily urine collection on the second day of hospitalization, using the immunonephelometric method. The patients were followed up for three months.*

Results: *MA was found in 24 of 52 (46.1%) acute stroke patients and in 5 of 37 (13.5%) controls ($p<0.05$). Patients with MA scored lower on the SSS than patients without MA, both on admission and later. We found a correlation between the daily excretion of albumin and the severity of neurological deficit on admission, as expressed by the SSS score ($r = –0.48$, $p<0.05$). The 90-day mortality rate was higher in patients with MA as compared to patients without MA (45.8% vs 7.1%). Patients with MA scored lower on the Barthel Index on Day 90 (median: 65 vs 100, $p<0.01$).*

Conclusion: *We found that MA can be detected in about 46% of non-diabetic patients with acute ischemic stroke. Measuring the albumin excretion rate may be a reliable predictor of increased mortality 3 months after stroke.*

BACKGROUND

Microalbuminuria (MA) is defined as a urinary albumin excretion rate of 30 to 299 mg/day [1]. Several studies have shown that MA in diabetic patients predicts diabetic nephropathy [2], as well as increased cardiovascular and overall mortality [2,3]. Persistent MA in diabetic patients correlates with the presence of hypertension [4], obesity, and dyslipidemia [5]. Hypertensive patients with MA more frequently develop left ventricle hypertrophy and renal insufficiency [6]. The relationship between the presence of MA and other atherosclerotic risk factors, such as hypertension [7,8], dyslipidemia [9] and smoking [10], is well documented in the general population as well. Several studies have revealed the significance of MA as a predictor of increased mortality in hypertensive patients [11], and in elderly persons [12].

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Correspondence address: Wojciech Turaj, Department of Neurology, Jagiellonian University, Collegium Medicum, ul. Botaniczna 3, 31-503 Kraków, Poland

MA is detected early in the course of acute myocardial infarction [13,14] and is considered an independent predictor of early mortality in this condition [14,15].

MA is thought to be a marker of widespread vascular damage [16]. It reflects the systemic transcapillary leakage of albumin [16], and is frequently accompanied by an increased activity of the von Willebrand factor and/or factor VII, both known to be markers of endothelial damage [17,18].

Little is known about the significance of MA in cerebrovascular diseases. Epidemiological studies suggest that MA can be regarded as a predictor of ischemic stroke in diabetic and non-diabetic subjects [19,20]. The thickness of the intima-media complex in carotid arteries, which reflects the progression of atherosclerosis in these vessels, correlates well with the presence of MA, as shown in a study by Mykkanen et al. [21]. Beamer et al. have recently proved that the prevalence of microalbuminuria is three-fold greater in patients with recent stroke when compared to controls with the same profile of cardiovascular risk factors [22].

Since there are no data available regarding the possible prognostic significance of MA in acute ischemic stroke patients, the aim of the study was to evaluate the prognostic significance of MA in non-diabetic acute stroke patients.

MATERIAL AND METHODS

Our research involved 52 patients (26 men and 26 women), aged from 41 to 89 years (mean age: 69.3±12.5), admitted to the Stroke Unit of the Neurological Department within 24 hours after stroke onset. In each case the diagnosis of stroke was confirmed by computer tomography (CT). The exclusion criteria were positive urinalysis including hematuria, leucocyturia, positive nitrite reaction, proteinuria, glycosuria, presence of diabetes mellitus, a history of inflammatory rheumatic disease, the presence of liver or neoplastic disease, or any sign of infection. The patient or caregiver was interviewed regarding past medical history to establish the presence of any risk factors for stroke, such as hypertension, ischemic heart disease, myocardial infarction, or smoking. The control group consisted of 37 age- and gender-matched subjects (12 men and 25 women), aged from 57 to 75 years (mean: 65.2±5.7), examined 3 to 18 months after acute stroke (median: 8 months). It has been widely reported that all hematological and biochemical disturbances which are recognized in the first few days after stroke onset disappear a few weeks later, so we decided to include in our control group patients more than 3 months after stroke.

All patients on admission (Day 0) had blood pressure and electrocardiogram (ECG) taken, and we noted the presence of atrial fibrillation. The severity of the neurological deficit was classified according to the Scandinavian Stroke Scale (SSS) [23] on Days 0, 1, 7, 14, and 30. The presence and severity of impaired consciousness were described according to the appropriate item in the SSS [23]. After discharge from the hospital (5 to 91 days after stroke onset, median=24 days) all survivors were followed for three months. The outcome measures on day 90 included mortality for any cause and the capacity to perform the activities of daily living (ADL) scored according to the Barthel Index [24].

Serum glucose levels were measured on admission and on Days 1, 2, 3, 5, 7, and 14. Glycosylated hemoglobin (HbA1) and fructosamine levels, hematocrit, white blood cell (WBC) count, urea, and lipids profile were taken on Day 1 after 12 hours of fasting.

Hematocrit and WBC were determined by an automated hematology analyzer (Cobas Vega Retic). The Blood glucose level and urea were determined by an automated chemistry analyzer (Hitachi 917). HbA1 was measured by high-performance liquid chromatography (Variant apparatus, Bio-Rad), and the serum fructosamine level was measured by the spectrophotometric method of Cobas Fara (Roche). Total cholesterol, HDL-cholesterol and triglycerides were assayed by the enzymatic method (CHOD-PAP) using commercially available kits (Boehringer-Mannheim; analyzer R A-1000). LDL-cholesterol was calculated by the Friedewald formula.

The albumin excretion rate was assessed in a 24-hour urine collection performed on Day 2. A 2-liter plastic container was used to collect the urine, and the volume was measured to the nearest 50 ml. The albumin concentrations were determined by an immunonephelometric technique with commercially available N antiserum to human albumin (DADE Behring), with a sensitivity of 8 mg/L, intra-assay coefficient of 4.3% and inter-assay coefficient of 4.4%. The albumin excretion rate was expressed as mg/24 hours. A daily urinary albumin excretion below 30 mg was considered to be within the normal range. MA was defined as an albumin urinary excretion rate between 30 and 299

Table 1. Urinary albumin excretion (UAE) in acute stroke patients.

	UAE (mg / 24 h) (median; 25th – 75th percentile)
Patients without MA [A]; n = 28	7.8 (6–14)
Patients with MA [B]; n = 24	86.8 (53.5–143)
Whole study group [A+B]; n = 52	25.5 (7.65–85.7)

MA - microalbuminuria

Table 2. Baseline characteristics and outcome in patients with microalbuminuria [A], without microalbuminuria [B], and in controls [C].

	With microalbuminuria A n=24	Without microalbuminuria B n=28	Controls C n=37
Age (years)*	73.3±11.6	66.0±12.4	65.2±5.5
Gender (males)	12 (50%)	14 (50%)	25 (67.5%)
History of hypertension	17 (70.8%)	16 (57.0%)	27 (73.0%)
History of ischemic heart disease	9 (37.5%)	15 (53.6%)	16 (43.3%)
History of myocardial infarction	0	1 (3.6%)	3 (8.1%)
ECG evidence of atrial fibrillation	10 (41.7%)#	2 (7.1%)	0
Death at 90 days	11 (45.8%)**	2 (7.1%)	
HbA1 (%) on Day 1	6.0±0.9	6.0 ± 1.2	
Fructosamine (mmol/l) on Day 1	275±34.3	272 ± 37	

#A-B - χ^2=8.68,p=0.0032; A-C - χ^2=13.02, p=0.0002
* A-B, A-C, B-C, p<0.05 (Student's t-test)
**A-B - χ^2=10.32, p=0.0013

mg/24 hrs. [25]. Proteinuria was defined as a urinary albumin excretion rate ⩾300mg/24 hrs. [25]

All controls were screened for stroke risk factors and were assessed for daily urinary albumin excretion rate, fasting serum glucose, WBC count, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

Statistical analysis

Normally distributed data are expressed as the mean±SD. The SSS scores and other data not normally distributed (Barthel Index score, albumin excretion rate) were reported as the median value with 25-75th percentiles. The Student's t-test, Chi-square test, Mann-Whitney U test, Wilcoxon matched pairs test and Spearman correlation were performed where appropriate. Statistical analysis was performed using the STATISTICA computerized statistical package for Windows.

Table 3. Scandinavian Stroke Scale scores (median value; 25th –75th percentile) in patients with microalbuminuria [A] and without microalbuminuria [B] (Mann –Whitney U test).

	With microalbuminuria A n=24	Without microalbuminuria B n=28
Day 0*	26; 9-38	39; 27-44
Day 1*	21; 10-40	39; 27-45
Day 7#	26; 10-42	46; 40-51
Day 14#	37; 25-46	50; 45-56
Day 30#	40; 28-50	55; 46-58

*A-B, p⩽0.05; #A-B, p⩽0.001

RESULTS

MA was found in 24 of 52 stroke patients (46.1%) and in 5 of 37 controls (13.5%) (p<0.05). Normal urinary albumin excretion was found in 28 stroke patients (53.9 %) and in 32 controls (86.5%), (p<0.05). The detailed values of daily urinary albumin excretion are shown in table 1.

When we separately analyzed patients with MA (group A), patients without MA (group B), and controls (group C), we found that the patients with MA were older than the patients without MA and the controls. A correlation between age and daily excretion of albumin in all stroke patients was found (r=0.45, p<0.01). No such correlation was found in the controls.

The 90-day mortality was higher in patients with MA as compared to patients without MA (45.8% vs. 7.1%).

More patients with MA showed evidence of atrial fibrillation on ECG than did those without MA or the controls. The study did not reveal any difference between patients with or without MA, or controls, according to gender, incidence of hypertension, ischemic heart disease, or myocardial infarction (table 2).

Patients with MA scored lower on the SSS than patients without MA, both on admission and later. During hospitalization, the neurological deficit in survivors from each group improved slightly (table 3). We found a correlation between the daily excretion of albumin and the SSS score on Day 0 in patients with MA (r=–0.48, p<0.05). Such a correlation was not found in patients without MA. There was a correlation between the SSS score and the age of the patients (r=–0.38, p<0.05), and there was a difference on Day 0 in terms of di-

minished consciousness between patients with and without MA (35.5% vs. 14.3% respectively, $p<0.05$).

We did not find any differences in the distribution of systemic complications recorded during hospitalization. Patients with MA scored lower on the Barthel Index on Day 90 than those without MA (median=65 vs. 100, $p\leqslant 0.01$).

The 90-day mortality rate was higher in patients with MA as compared to patients without MA (45.8% vs. 7.1%; $p<0.05$).

DISCUSSION

MA has traditionally been a marker for monitoring diabetes mellitus [26,27] Our study is the first to evaluate the prognostic significance of MA in non-diabetic acute stroke patients. In our study we noted with interest the very high prevalence of MA (about 46%) in non-diabetic acute stroke patients, as opposed to only 13.5% of the controls, who were several months after their stroke. Interestingly, a similar very high prevalence of microalbuminuria in stroke patients was noted by Beamer at al, who found microalbuminuria in about 30% of stroke patients and in 10% of controls matched for stroke risk factors [22].

An increased albumin urinary excretion rate is two- to four-fold less likely to occur in the general population than in non-diabetic acute stroke patients [25] The prevalence of MA varies widely between ethnic groups, and ranges from 2.2% to 10.2% in Britain [11,28], up to 39% and 42% in Aboriginal women and men respectively [29]. It has been documented in several studies that MA in the general population correlates with factors that increase the risk for atherosclerotic diseases, such as high blood pressure [30], obesity [25], high triglyceride levels [7], low HDL cholesterol levels [25], raised serum insulin levels [7,30] and carotid artery (intima+media) thickness [21].

MA in the diabetic population is a predictor of the development of persistent clinical proteinuria, consequent renal disease, and increased risk of cardiovascular death [1]. Mykkanen et al, in a study of 1449 patients aged from 40 to 69 years, showed a higher prevalence of MA in diabetic than in non-diabetic patients (27.6 vs. 13.9%) [21]. In the present study we excluded patients with diabetes mellitus in order to obtain a group of patients without the additional risk of cardiovascular death related to MA in the course of diabetes mellitus.

In the non-diabetic population, MA is seen in patients with atherosclerotic vascular diseases, such as hypertension [31], coronary artery disease [11], peripheral arterial diseases [11], and obesity [31]. The mechanism underlying MA in this population remains unknown, but Kofoed-Enevoldsen et al. proposed that MA in the non-diabetic population is associated with the loss of glomerular charge selectivity due to the loss of heparan sulfate [32]. The latter is thought to be a non-specific marker of widespread vascular damage or of endothelial dysfunction [18].

Very few clinical reports have documented that MA is a risk factor for ischemic stroke. Miettinen et al, in a study of 1375 non diabetic and 1056 diabetic patients with a seven-year follow-up, showed that proteinuria (>150mg/L) in diabetic patients doubles the risk for vascular accidents. The risk of stroke, both in patients with diabetes mellitus and in non-diabetics, was higher with proteinuria >300mg/L [19]. Many clinical studies have identified MA as a risk factor for death, independent of classic cardiovascular risk factors, not only in patients with non insulin-dependent diabetes mellitus [2,3,33], but also in non-diabetics [11]. The prognostic significance of MA in a non-diabetic acute stroke population has not previously been studied.

Our data indicate a very high prevalence of MA in acute stroke when compared to age- and gender-matched controls, the latter being assessed several months after stroke. Data concerning the prevalence of MA in the non-diabetic Polish population are not available.

In our group of patients with acute stroke, the high prevalence of MA could be related to the very common presence of hypertension or ischemic heart disease; however, when we compared patients with and without MA we did not find any differences in the distribution of these stroke risk factors among the two group. We also did not find a high prevalence of MA in the controls, despite the fact that they had a similar distribution of stroke risk factors, that is hypertension and ischemic heart disease.

Based on the evidence from studies on patients with acute myocardial infarction, MA in the acute phase of stroke may be a marker of the inflammatory response. Berton at al, in a study of 360 patients with acute myocardial infarction and 136 controls, found a significantly higher albumin excretion rate on both the first and third day after myocardial in-

farction, than in the control group. No difference in the albumin excretion rate between patients with myocardial infarction and controls was present on the seventh day [14]. In our study, MA in acute stroke patients was assessed on Day 2, and we may speculate that the increase is due at least partly to an acute phase inflammatory response. According to Gosling et al, MA in acute myocardial infarction is a consequence of the inflammatory reaction that accompanies acute myocardial infarction, and involves the renal vascular system [13]. The adverse relation between mortality and MA found in patients with acute myocardial infarction supports the probability of a similar relation in the acute phase of stroke. An albumin excretion rate >50mg/24 hours significantly increases the risk of death in patients with acute myocardial infarction. Berton et al. showed that among 26 patients with acute myocardial infarction who died during hospitalization, MA was present in 24 [14].

The significant correlation we discovered between MA on Day 2 and the neurological deficit in the SSS score on Day 0 ($r=-0.41$, $p\leq0.001$) and on Day 1 ($r=-0.35$, $p\leq0.001$) supports the argument that MA reflects the severity of stroke and is a marker of the acute inflammatory response.

Another feature of our study was the correlation between the greatly older age of patients with MA compared to patients with a normal albumin excretion rate. There are only a few studies examining the influence of age on the albumin excretion rate in the general population, but most authors seem to be in agreement that urinary albumin concentrations may decline with age [31]; however, a recently published study shows that age is an independent factor for the presence of microalbuminuria in stroke patients [22]. In our study this strong correlation between age and MA may not necessarily represent a cause-effect relationship, but may be due to the phenomenon of older patients having a worse neurological deficit, which also strongly correlates with age.

The relation between increased albumin excretion rate, lower outcome test scores, and a higher 90-day mortality rate may be related to the more advanced age of patients with increased albumin excretion, or to the worse neurological deficit during the course of the disease, or both. Whether MA is an independent prognostic indicator of poor outcome in stroke patients remains to be established.

CONCLUSIONS

We have shown that MA was found in about 46% of non-diabetic acute ischemic stroke patients. Measuring the albumin excretion rate in the acute phase of stroke may be a reliable predictor of higher mortality 3 months after stroke.

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