HIGH LIGHT

Micro- and macroalbuminuria predict hemorrhagic transformation in acute ischemic stroke

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Abstract—*Background:* Hemorrhagic transformation (HT) after cerebral ischemia seems to be related to the endothelial disruption secondary to the ischemic process. Albuminuria has recently been found to be a marker of chronic endothelial damage. *Objective:* To investigate the relationship between albuminuria and HT in patients with acute ischemic stroke. *Methods:* We studied 200 patients (51.5% men, age 72.5 ± 8.5 years) with ischemic stroke within the first 24 hours of evolution. HT development was assessed on CT performed between days 4 and 7 of evolution and classified according to the ECASS II criteria. Urinary samples were collected within the first 3 hours after admission and the presence of albuminuria, which was considered to be present when the ratio albumin-to-creatinine was ≥30 mg/g creatinine, was determined by nephelometry within the first 24 hours of evolution. *Results:* Forty-nine patients (24.5%) had albuminuria and 36 (18%) had HT on the second CT scan. After adjusting for potential confounders including a previous history of diabetes mellitus, hypertension and atrial fibrillation, stroke severity, the presence of early signs of ischemia and leukoaraiosis on the baseline CT scan, and IV anticoagulant treatment, logistic regression analysis showed that albuminuria was independently associated with HT (OR, 7.45; 95% CI 2.30 to 24.16). Moreover, albuminuria was also a significant and independent predictor of parenchymal hemorrhage type 1 and 2 (OR, 8.30; 95% CI 1.77 to 38.89). *Conclusion:* Albuminuria is an independent predictor of hemorrhagic transformation, and particularly of the most severe bleedings, in patients with acute ischemic stroke. Due to the small number of events, the predictive capacity of albuminuria should be confirmed in larger studies.

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Albuminuria has been identified as a strong marker of stroke risk,[1,2] coronary heart disease,[3-5] and death,[4,6] independently of renal function, hypertension, and diabetes. The risk persists even with very low levels of microalbuminuria.[4] Albuminuria also predicts prognosis, as temporary increases of urinary albumin excretion in the acute phase of myocardial infarction[7,8] and stroke[9,10] have been reported to be associated with a poor outcome.

The dysfunction of vascular endothelium may be a link between albuminuria and increased risk of cardiovascular disease. In fact, the association between albuminuria and endothelial dysfunction has been previously reported.[11,12] Since the endothelial disruption is the main mechanism related to the development of hemorrhagic transformation (HT) after cerebral ischemia, albuminuria might be a predictor of secondary bleeding in patients with ischemic stroke.

In this study we sought to determine whether the presence of micro- or macroalbuminuria in patients with acute ischemic stroke might be a predictive factor of HT of cerebral infarction.

Methods. This prospective study included 383 patients with ischemic stroke within the first 24 hours from symptoms onset between March 2001 and October 2002. At a later time, 49 patients without a known time for onset of symptoms, 74 patients with brainstem ischemic stroke, 2 patients with renal insufficiency, and 5 patients with severe diabetic nephropathy were excluded. Thirty-seven patients who took part in neuroprotection clinical trials and 16 patients treated with tissue plasminogen activator (tPA) were also excluded. In total, 200 patients were enrolled in the study. The protocol was approved by the ethics committee and written informed consent was given by patients or their relatives.

Medical history recording vascular risk factors, blood coagulation and chemistry tests, 12-lead ECG, chest radiography, and ultrasonographic arterial supra-aortic trunk examination were performed in all patients.

Stroke severity was quantified at admission by an experienced neurologist using the National Institute of Health Stroke Scale (NIHSS).[13] Outcome at 3 months was evaluated using the modified Rankin scale (mRS).

CT scan was carried out at admission and repeated between days 4 and 7 after stroke onset, or before if the patient had neurologic deterioration which was defined as an increase ≥4

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Table 1 *Baseline clinical characteristics, vascular risk factors, stroke subtype, biochemical parameters, neuroimaging findings, and outcome in patients with and without albuminuria*

	Albuminuria (–), n = 151	Albuminuria (+), n = 49	*p*
Age, y	71.9 ± 8.7	72.1 ± 7.9	0.980
Men, n (%)	80 (53.0)	23 (46.9)	0.462
Time from onset, h	7.7 (4.7–15.6)	6.7 (4.1–10.1)	0.584
Vascular risk factors, n (%)			
History of diabetes	40 (26.5)	24 (49.0)	0.003
History of hypertension	63 (41.7)	28 (57.1)	0.060
History of atrial fibrillation	67 (44.4)	28 (57.1)	0.120
Clinical characteristics			
NIHSS on admission	13 (6–18)	14 (8–16)	0.709
Stroke subtype, n (%)			0.183
Atherothrombotic	59 (39.1)	17 (34.7)	
Cardioembolic	56 (37.1)	25 (51.0)	
Small vessel disease	29 (19.2)	4 (8.2)	
Cryptogenic	7 (4.6)	3 (6.1)	
Biochemistry and vital signs on admission			
Body temperature (ºC)	36.9 ± 0.6	36.9 ± 0.7	0.116
Systolic blood pressure (mm Hg)	175 (158–190)	197 (182–209)	0.017
Diastolic blood pressure (mm Hg)	85 (78–95)	95 (85–105)	0.337
Glucose levels (mg/dL)	139 (116–179)	193 (142–256)	<0.0001
Fibrinogen (mg/dL)	371 (262–422)	359 (319–481)	0.784
Leukocyte count ($\times 10^3/mm^3$)	6.5 (5.1–8.1)	6.6 (5.1–8.8)	0.615
Platelet count ($\times 10^3/mm^3$)	151 (91–205)	178 (142–232)	0.541
APTT (sec)	27.6 ± 3.3	25.7 ± 3.1	0.640
Neuroimaging findings			
Early signs of brain infarction, n (%)	41 (27.2)	26 (53.1)	0.001
Leukoaraiosis, n (%)	37 (24.5)	34 (69.4)	<0.0001
Infarct volume (cc)	93 (45–174)	151 (101–174)	<0.0001
Hemorrhagic transformation, n (%)	14 (9.3)	22 (44.9)	<0.0001
Severe hemorrhagic transformation, n (%)	3 (2.0)	10 (20.4)	<0.0001
Outcome			
Rankin at 3 months	2 (1–3)	4 (3–5)	<0.0001

Values represent mean ± SD, n (%), or median (range).

NIHSS = NIH Stroke Scale.

points in the NIHSS between admission and 72 hours of evolution. The presence of leukoaraiosis and early CT signs of infarction, which included the presence of focal hypodensity consistent with the clinical picture, obscuration of the lenticular nucleus, obscuration of the cortex, and mass effects with effacement of the cortical sulci or shifting of the structures of the median line, were evaluated in the first radiologic examination. The infarct volume and the presence of HT were evaluated in the second CT scan. Infarct volume was calculated by using the formula $0.5 \times a \times b \times c$ (where a and b are the largest perpendicular diameter measures on CT and c is the slice thickness). The HT was classified according to the ECASS II criteria[14] as follows: hemorrhagic infarction type 1 (HI1) was defined as small petechiae along the margins of the infarct, HI type 2 (HI2) was defined as more confluent petechiae within the infarct area but without space-occupying effect, parenchymal hemorrhage type 1 (PH1) was defined as blood clots not exceeding 30% of the infarct with some mild space-occupying effect, and PH type 2 (PH2) as blood clots exceeding 30% of the infarct area with significant space-occupying effect. PH1 and PH2 groups were considered to have severe HT. All CT evaluations were made by the same neuroradiologist who had no knowledge of the patients' clinical and biochemical results.

According to the TOAST criteria[15] stroke subtype was classified as atherothrombotic, cardioembolic, small vessel disease, and cryptogenic. Only patients who had a systolic blood pressure (SBP) ≥ 220 mm Hg or a diastolic blood pressure (DBP) ≥ 120 mm Hg received hypotensive drugs in the first 48 hours after admission. Insulin was administered in case of hyperglycemia (blood glucose > 160 mg/dL) and metamizol or paracetamol was given in case of hyperthermia (tympanic temperature >37.5°). Subcutaneous low-dose heparin as a prophylaxis against pulmonary thromboembolism and antiplatelet drugs were prescribed early after hospitalization. IV heparin was given within the first 24 hours from onset to patients with a major cardioembolic source but not as treatment for progressing stroke. Treatment with IV heparin was initiated with a total dose of 400 IU/kg/day and APTT

Table 2 *Baseline clinical characteristics, vascular risk factors, stroke subtype, biochemical parameters, and neuroimaging findings in patients with and without hemorrhagic transformation*

	Nonhemorrhagic transformation, n = 164	Hemorrhagic transformation, n = 36	*p*
Age, y	72.6 ± 8.3	72.3 ± 9.4	0.275
Men, n (%)	85 (51.8)	18 (50.0)	0.842
Time from onset, h	6 (4.5–9)	7 (4.7–11.4)	0.193
Vascular risk factors, n (%)			
History of diabetes	42 (25.6)	22 (61.1)	<0.0001
History of hypertension	61 (37.2)	30 (83.3)	<0.0001
History of atrial fibrillation	64 (39.0)	31 (86.1)	<0.0001
Clinical characteristics			
NIHSS on admission	10 (7–16)	13 (8–17)	0.184
Cardioembolic stroke, n (%)	55 (33.5)	26 (72.2)	<0.0001
IV heparin prior to second CT, n (%)	62 (37.8)	28 (77.8)	<0.0001
Biochemistry and vital signs on admission			
Body temperature (ºC)	36.8 ± 0.7	37.2 ± 0.7	0.576
Systolic blood pressure (mm Hg)	172 (153–184)	190 (172–204)	<0.0001
Diastolic blood pressure (mm Hg)	86 (76–95)	90 (85–100)	0.032
Glucose levels (mg/dL)	138 (116–170)	224 (196–284)	<0.0001
Fibrinogen (mg/dL)	360 (319–415)	361 (319–424)	0.621
Leukocyte count ($\times 10^3/mm^3$)	6.4 (5.2–8.3)	6.7 (5.1–8.9)	0.521
Platelet count ($\times 10^3/mm^3$)	163 (135–212)	174 (138–220)	0.863
APTT (sec)	25.9 ± 2.9	26.1 ± 2.9	0.532
Albuminuria, n (%)	27 (16.5)	22 (77.8)	<0.0001
Neuroimaging findings, n (%)			
Early signs of brain infarction	37 (22.6)	30 (83.3)	<0.0001
Leukoariosis	49 (29.9)	22 (61.1)	<0.0001

Values represent mean ± SD, n (%), or median (range).

NIHSS = NIH Stroke Scale.

controls were performed every 6 hours (APTT therapeutic target value, 1.8 to 3.2 of control). Coagulation tests were repeated once the presence of HT was confirmed.

Laboratory tests. We determined the presence of albuminuria by analyzing the first available urine sample, which was obtained from all patients within the first 3 hours following admission to the emergency department, either from spontaneous urination or by ureteral catheterization, if necessary. The urine sample was refrigerated and stored at 4 °C until processed in the laboratory, which always took place within 24 hours. In order to determine the urinary-to-creatinine ratio, the urinary albumin excretion rate was calculated using a nephelometric procedure with a specific anti-albumin monoclonal antibody, and urinary creatinine was assessed using the Jaffe method. Albumin and creatinine concentrations are expressed in mg/L and g/L, respectively. Thus, the urinary albumin-to-creatinine ratio is expressed in mg/g. In accordance with the recommendations of the American Diabetes Association[16] and the National Kidney Foundation,[17] an albumin-to-creatinine ratio <30 mg/g creatinine was considered to be normal whereas albuminuria was considered to be present when the albumin-to-creatinine ratio was ≥30 mg/g creatinine. An albumin-to-creatinine ratio between 30 and 300 mg/day creatinine defines the microalbuminuric range whereas an albumin-to-creatinine ratio >300 mg/day creatinine is considered to be indicative of macroalbuminuria. For a sensitivity analysis, albumin concentrations were also determined in urine of 24 hours during the first week of hospitalization in 194 patients.

Statistical analysis. Proportions between groups were compared using the χ^2 test. Continuous variables have been expressed as mean ± SD or median and quartiles, depending on whether they were normally distributed, and compared using Student *t* test or the Mann-Whitney test, as appropriate. Spearman's correlation was used to compare albumin concentrations in the first available urine sample after admission and in urine of 24 hours during the first week. The importance of micro and macroalbuminuria for the development of HT was assessed by logistic regression analysis, adjusting for those baseline variables related to HT in the bivariate analyses. The model was further adjusted for the ultimate volume of hypodensity on CT. Moreover, the interactions between albuminuria and these variables were tested.

Results. Forty-nine patients (24.5%) had albuminuria in the first available sample. Forty-four (90%) had microalbuminuria whereas the remaining 5 patients (10%) had macroalbuminuria. Microalbuminuria was found in 47 patients in urine of 24 hours. There was a very high correlation between albumin concentrations in the two samples (Spearman coefficient, 0.98). Table 1 shows the main characteristics and outcome of patients with and without albuminuria. A previous history of diabetes was significantly more frequent and systolic and diastolic blood pressures were significantly higher at admission in patients with albuminuria. Early CT signs of ischemia and the presence of leukoaraiosis were more frequent in patients with albuminuria, who also developed larger infarct volumes, pre-

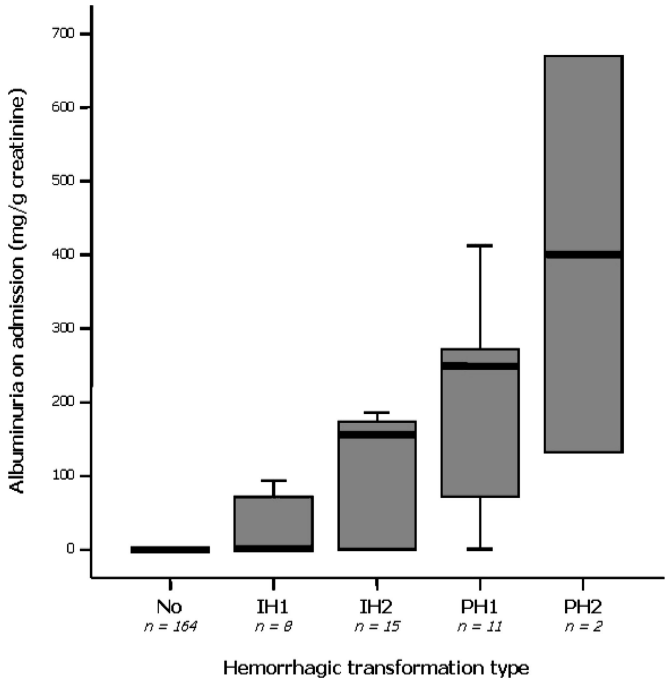

Figure. Boxplots show median values (horizontal line inside the box), quartiles (box boundaries), and the largest and smallest observed values (lines drawn from the end of the box) of albumin-to-creatinine ratio. HT = hemorrhagic transformation; HI-1 = hemorrhagic infarction type 1; HI-2 = hemorrhagic infarction type 2; PH-1 = parenchymal hematoma type 1; PH-2 = parenchymal hematoma type 2.

sented a greater percentage of HT, and had a worse prognosis at 3 months.

Thirty-six patients (18%) showed HT on the second CT scan (IH1, 8; IH2, 15; PH1, 11; PH2, 2). HT was more frequent in patients with a previous history of diabetes, high blood pressure, atrial fibrillation, and cardioembolic stroke, and in those patients who received IV heparin after admission (table 2). The APTT determined following confirmation of HT was 42.2 ± 13.6 seconds compared to 41.7 ± 17.8 seconds at 48 hours in patients treated with IV heparin without HT. No patient had APTT greater than 3.5 of control. None of the patients developed HT outside the ischemic territory.

Glucose levels and systolic and diastolic blood pressure at admission were significantly higher, and early signs of ischemia and leukoaraiosis significantly more frequent, in patients with HT. Albuminuria was also more frequent in patients with secondary bleeding (78% vs 15.5%, $p < 0.0001$) and the higher the severity of the bleeding the greater the albumin-to-creatinine ratio (figure).

Logistic regression analysis showed that albuminuria was independently associated with HT (OR, 7.4; 95% CI, 2.3 to 24.2) after adjustment for the history of diabetes, hypertension and atrial fibrillation, stroke severity, presence of early signs of ischemia and leukoaraiosis, and the administration of IV heparin prior to the second CT (table 3). The OR of HT for albuminuria did not substantially change after a further adjustment for the ultimate hypodensity volume on CT (OR, 6.8; 95% CI, 2.2 to 21.8). The interaction between albuminuria and the history of diabetes ($p = 0.019$) and hypertension ($p < 0.001$) was significant, so the OR of HT for albuminuria was calculated separately for the two categories of these vascular risk factors. Hence, among patients with hypertension (OR, 15.1; 95% CI, 3.1 to 73.2) and without history of diabetes (OR, 14.3; 95% CI, 2.8 to 74.2) albuminuria on admission was associated with a higher risk of HT. In contrast, a non significant effect was found in patients with diabetes (OR, 4.6; 95% CI, 0.9 to 22.4; $p = 0.057$) and no effect was found in those without history of hypertension. When the clinical variables (systolic and diastolic BP, serum glucose, and cardioembolic stroke) instead of the history of the risk factors were included in the model, the OR of the albuminuria for HT was 3.30 (95% CI, 1.03 to 10.57). Albuminuria was also a significant and independent predictor of severe HT (PH1 or PH2) (OR, 8.30; 95% CI, 1.77 to 38.89) after adjustment for the same potential confounders.

Table 3 *Adjusted ORs of hemorrhagic transformation*

Independent variables	OR	95% CI	*p*
History of diabetes	2.33	0.75–7.21	0.141
History of hypertension	4.07	1.13–14.66	0.032
History of atrial fibrillation	5.96	1.37–25.83	0.017
Stroke severity	0.92	0.68–1.23	0.581
Albuminuria	7.45	2.30–24.16	0.001
Early signs of brain infarction	11.40	3.24–40.02	<0.0001
Leukoariosis	1.40	0.44–4.93	0.563
IV heparin prior to second CT	2.09	0.52–8.41	0.298

Discussion. The presence of albuminuria in the first urine sample obtained on admission in patients with acute hemispheric ischemic stroke is an independent risk factor of HT of cerebral infarction. Furthermore, albuminuria increases eightfold the risk of severe HT. Although in 90% of patients with albuminuria, the levels were in the microalbuminuric range, the degree of albuminuria was related to the severity of the HT.

The mechanism by which micro and macroalbuminuria are associated with HT of ischemic stroke is not well known. According to the Steno hypothesis,[11] albuminuria is a marker of micro- and macroangiopathy. The loss of heparan sulfate from the extracellular matrix and plasma membrane can lead to increased permeability in vascular membranes and can increase the collection of atherogenic particles in the arterial walls. This process is accompanied, or even preceded, by endothelial dysfunction that is present in diabetic[18] and hypertensive[19] patients with microalbuminuria.[20] The interaction between albuminuria and the history of diabetes and hypertension on HT likely reflects that the predictive capacity of albuminuria is associated with endothelial damage rather than with glomerular disturbances.

In some patients, the microalbuminuria detected in the acute phase of ischemic stroke can be a transient acute phase reactant[9,21,22] and, consequently,

not a biomarker of angiopathy in contrast to persistent microalbuminuria or macroalbuminuria.[11,18,19] However, in the present study, albuminuria was associated with HT after adjustment for stroke severity and ultimate infarct volume, so we may reasonably rule out a predictive effect as an epiphenomenon of the stress response. Although HT in patients with stroke with transient microalbuminuria cannot be attributed to a prior vascular lesion, a link has been demonstrated between microalbuminuria and elevated biomarkers of the inflammatory reaction in blood.[23] This association might facilitate the development of HT during the acute phase of cerebral infarction.[24]

Albuminuria is an important risk factor for vascular complications and poor prognosis after vascular events.[1-6] This effect is found at urine concentrations between 30 and 300 mg/24 hours, which cannot be detected by conventional urine tests,[25] so sensitive and reliable techniques such as nephelometry are needed.[26] The diagnosis of microalbuminuria requires its determination in two or three urine samples taken in a period of 24 hours.[27] However, this study found that the concentration of albumin in the first available urine sample correlates well with the 24 hours absolute urinary albumin concentration, as has been previously reported.[17,28] Another limitation of this study is that factors that may influence microalbuminuria detection, such as urinary infection, prostate or vaginal conditions, congestive heart failure, or exercise, were not recorded.[29] However, our objective was not to study microalbuminuria in patients with acute stroke, but rather to determine the value of an isolated and early determination of albuminuria as a risk marker of HT in patients without renal diseases. Finally, we have analyzed a large number of predictor variables for a model with only 36 outcomes, so the robustness of our results should be confirmed in a larger study.

A further point of interest is the potential value of microalbuminuria in patients treated with reperfusion therapies. Our series does not permit us to draw definitive conclusions, but among the 16 patients treated with tissue plasminogen activator not included in this study, three patients out of five who showed microalbuminuria, and only one of those who did not, developed HT ($p = 0.063$).

Although these results need confirmation, albuminuria might be a useful biomarker of HT in the acute phase of ischemic stroke, particularly in nondiabetic patients and in those with history of hypertension. The predictive value may be similar to that of other serum markers like metalloproteinase-9,[24,30] cellular fibronectin,[31] thrombin-activable fibrinolysis inhibitor,[32] and plasminogen activator inhibitor-I.[32] The hypothesis of microalbuminuria as a marker of endothelial brain dysfunction that results in a systemic transvascular leakiness of macromolecules may have therapeutic implications. In fact, it has been demonstrated that a low-protein diet and the reduction of cholesterol levels, glycosylated hemoglobin, and systolic blood pressure levels reduces microalbuminuria,[5,33] so these actions may prevent HT in patients with ischemic stroke.

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