

# Insulin Resistance Is Associated With a Poor Response to Intravenous Thrombolysis in Acute Ischemic Stroke

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**OBJECTIVE**—Insulin resistance (IR) may not only increase stroke risk, but could also contribute to aggravate stroke prognosis. Mainly through a derangement in endogenous fibrinolysis, IR could affect the response to intravenous thrombolysis, currently the only therapy proved to be efficacious for acute ischemic stroke. We hypothesized that high IR is associated with more persistent arterial occlusions and poorer long-term outcome after stroke thrombolysis.

**RESEARCH DESIGN AND METHODS**—We performed a prospective, observational, longitudinal study in consecutive acute ischemic stroke patients presenting with middle cerebral artery (MCA) occlusion who received intravenous thrombolysis. Patients with acute hyperglycemia ( $\geq 155$  mg/dL) receiving insulin were excluded. IR was determined during admission by the homeostatic model assessment index (HOMA-IR). Poor long-term outcome, as defined by a day 90 modified Rankin scale score  $\geq 3$ , was considered the primary outcome variable. Transcranial Duplex-assessed resistance to MCA recanalization and symptomatic hemorrhagic transformation were considered secondary end points.

**RESULTS**—A total of 109 thrombolysed MCA ischemic stroke patients were included (43.1% women, mean age 71 years). The HOMA-IR was higher in the group of patients with poor outcome ( $P = 0.02$ ). The probability of good outcome decreased gradually with increasing HOMA-IR tertiles (80.6%, 1st tertile; 71.4%, 2nd tertile; and 55.3%, upper tertile). A HOMA-IR in the upper tertile was independently associated with poor outcome when compared with the lower tertile (odds ratio [OR] 8.54 [95% CI 1.67–43.55];  $P = 0.01$ ) and was associated with more persistent MCA occlusions (OR 8.2 [1.23–54.44];  $P = 0.029$ ).

**CONCLUSIONS**—High IR may be associated with more persistent arterial occlusions and worse long-term outcome after acute ischemic stroke thrombolysis.

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Stroke is the second most common cause of death and the first leading cause of disability in adults worldwide. Moreover, stroke burden is expected to increase rapidly in the following decades (1). Approximately 85% of all strokes are ischemic, mainly caused by acute thromboembolic occlusion of intracranial arteries. In this context, reperfusion therapies focus on early vessel reopening to save cerebral ischemic tissue

at risk, thus reducing final infarct size and neurologic sequelae. Currently, intravenous thrombolysis with tissue plasminogen activator (tPA) remains the only therapy that has proved efficacy for acute ischemic stroke.

Insulin resistance (IR), the proposed main pathophysiological mediator of metabolic syndrome (2), may lead to a prothrombotic and proinflammatory state, characterized by a derangement in

endogenous fibrinolysis and increased platelet activation (3). These deleterious effects may contribute to explain the well-known association between raised IR and a higher incident or recurrent stroke (4), but whether IR-related metabolic disturbances may also have an impact on the prognosis of acute ischemic stroke once it has occurred and on the response to intravenous thrombolysis remains largely unknown. In this setting, our group previously reported that acute stroke patients fulfilling criteria for metabolic syndrome showed a higher resistance to intravenous thrombolysis (5,6). However, that study was based only on metabolic syndrome clinical criteria and no direct measure to assess IR was performed, thus we could not draw any valid conclusion regarding the relationship between IR and acute stroke outcome. Considering the pathophysiological background and our previous research, we designed a prospective study to test the hypothesis that a high IR is associated with a worse clinical outcome and more persistent arterial occlusions after intravenous thrombolysis for acute ischemic stroke.

## RESEARCH DESIGN AND METHODS

### Patient selection

We prospectively studied consecutive acute nonlacunar middle cerebral artery (MCA) ischemic stroke patients admitted to our Stroke Unit from 2008 January to 2010 July who fulfilled criteria to receive intravenous thrombolysis according to our institutional protocol in a standard dose of 0.9 mg/kg. Specific additional inclusion criteria for this study comprised 1) MCA occlusion on prebolus transcranial color coded Duplex (TCCD) examination, 2) availability of blood samples to determine fasting insulin 24 to 48 h after admission, 3) no chronic treatment with insulin before qualifying stroke, and 4) admission glycemia of  $< 155$  mg/dL. This cutoff point of glycemia is used in our institutional protocol as a target for active treatment with insulin according to the results

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of the glycemia in acute stroke (GLIAS) study (7) and also in agreement with American Diabetes Association's consensus on inpatient glycemic control (8). The GLIAS study identified a glycemia  $\geq 155$  mg/dL as an independent predictor of poor outcome in acute stroke patients. By excluding patients with hyperglycemia  $>155$  mg/dL in our study we intended to avoid exogenous insulin administration before blood sampling and also to attenuate the confounding effect of hyperglycemia on stroke outcome.

Between 2008 January and 2010 July, 193 ischemic stroke patients were treated with intravenous thrombolysis in our Stroke Unit. Of them, 41 were excluded due to hyperglycemia at admission and 12 were not MCA territory ischemic strokes. Of the remaining 140, 115 showed MCA occlusions on prebolus TCCD examination. Finally, fasting insulin could be determined in 109 MCA ischemic stroke patients who could be included. The study protocol was approved by the local ethics committee, and informed consent to participate in our study was obtained from all patients or their relatives.

### **Clinical assessment**

All included patients underwent medical history, physical examination, routine blood biochemistry and blood count, electrocardiogram (ECG), chest X ray, urgent cervical Duplex ultrasound and transcranial Doppler and/or Duplex examinations, and noncontrast brain computed tomography (CT) upon admission to our Stroke Unit. Intravenous thrombolysis was administered in a 0.9 mg/kg tPA dose as described in Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) (9).

Prebolus systolic and diastolic blood pressure (BP) values, temperature, and glycemia were determined on admission. Neurologic examinations were performed on admission and periodically during the next 24 h after the initiation of the thrombolytic infusion. Stroke severity was determined with the National Institutes of Health Stroke Scale (NIHSS) (10).

During admission, history of vascular risk factors and vascular disease was obtained. Cerebral CT scans were carried out before tPA bolus and repeated after 24 h, or earlier when neurologic deterioration occurred. Early ischemic changes in each patient's CT were evaluated according to the Alberta Stroke Program Early

CT Score (ASPECTS) (11). This is a 10-point quantitative topographic CT scan score developed to assess early ischemic changes on pretreatment CT studies in patients with acute ischemic stroke of the anterior circulation. A normal CT scan receives ASPECTS of 10 points, whereas a score of 0 indicates massive involvement throughout the MCA territory.

On follow-up CT we measured infarct volume by using the formula for irregular volumes and we also assessed the presence of symptomatic hemorrhagic transformation during admission, according to the SITS-MOST definition: local or remote parenchymal hemorrhage type 2—blood clot exceeding 30% of the infarct area, with substantial space occupation—on the imaging scan at 22–36 h after treatment, combined with a neurologic deterioration of four or more points on the NIHSS from baseline, or from the lowest NIHSS score between baseline and 24 h, or leading to death.

Stroke subtypes were classified using modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (12), in agreement with the results of the additional diagnostic procedures performed (echocardiography, ECG–Holter monitor, special coagulation test, and immunologic study).

Clinical long-term outcome was assessed 90 days after symptoms onset by means of the modified Rankin Scale (mRS) (13). A mRS score  $\leq 2$  determined on day 90 after stroke onset was considered indicative of good long-term functional outcome.

### **Measurement of IR**

IR was quantified with the homeostatic model assessment index (HOMA-IR) following the formula described by Matthews et al. (14):  $\text{HOMA-IR} = \text{glucose mg/dL} \times \text{insulin mU/L} / 405$ . Fasting blood samples were drawn 24–48 h after admission to our Stroke Unit. Serum was immediately separated by centrifugation at 3,500 revolutions per minute for 15 min. Right away the insulin level was measured with a commercial enzyme-linked immunosorbent assay (ARCHITECT insulin assay; Abbott, Wiesbaden, Germany) and expressed in milliunits per liter; glucose was measured in serum using standardized methods and expressed in milligrams per deciliter. Determinations were performed in duplicate, and the mean value of both determinations was used. The mean intra-assay coefficients of variation were  $<10\%$  in all cases.

### **Transcranial ultrasound assessment of resistance to clot lysis**

All extracranial ultrasound imaging and transcranial Duplex were performed with a Toshiba Aplio XG echograph (Toshiba Medical Systems Europe, Zoetermeer, the Netherlands). Transcranial Doppler examinations were conducted with a power-M-mode-equipped Sonara device (Viasys Healthcare). Standard transcranial Doppler (TCD) and/or TCCD examinations were performed in our Stroke Unit, right before tPA infusion to check the existence of MCA occlusion. If the patient had an inappropriate acoustic window, a single bolus of echocontrast agent (Sonovue) was administered. A follow-up TCD or TCCD study was performed by the same neurosonologist 1 and 24 h after intravenous tPA bolus to monitor arterial status.

MCA occlusions were defined according to the Thrombolysis in Brain Ischemia (TIBI) grading system (15), which establishes grade 0 (absent), 1 (minimal), 2 (blunted), or 3 (dampened) as indicative of arterial occlusion. Arterial recanalization was diagnosed when the end-diastolic flow velocity increased (TIBI grade 4) or became normal (TIBI grade 5). Resistance to clot lysis was defined by the lack of complete arterial recanalization (TIBI 4–5) in the 24-h control transcranial ultrasound examination.

### **Statistical analysis**

Statistical analyses were performed with the SPSS statistical package (version 17.0; SPSS, Chicago, IL). Statistical significance for intergroup differences was assessed by the  $\chi^2$  test for categorical variables and the Student *t* test and Mann-Whitney *U* test for continuous variables. All continuous variables except NIHSS score, ASPECTS score, leukocyte, and platelet were normally distributed. Long-term clinical outcome was considered the primary outcome variable, whereas resistance to clot lysis, symptomatic hemorrhage transformation, and final infarct volume were considered secondary end points. To evaluate the relationship between IR (HOMA-IR), poor clinical outcome, hemorrhagic transformation, infarct volume, and resistance to clot lysis, multivariate adjusted logistic regression models were applied when significant differences in respective bivariate analysis were observed. Variables showing a  $P < 0.1$  on the respective bivariate analysis were included in those models. Moreover, we computed age-, sex-, and other significant variables—adjusted odds ratios (ORs) for poor clinical outcome and resistance to

**Table 1—Demographic and baseline variables in the whole study sample and across the group of patients belonging to the top HOMA-IR tertile and remaining tertiles**

Variables	All (n = 109)	Upper tertile (n = 38)	Rest of tertiles (n = 71)	P value
Sex, female (%)	47 (43.1)	18 (47.4)	29 (40.8)	0.512
Age (years)	71.0 ± 11.3	70.57 ± 12.49	71.23 ± 10.76	0.774
Smoking (%)	28 (25.7)	9 (23.7)	19 (26.8)	0.726
Ethanol abuse (%)	9 (8.3)	1 (2.6)	8 (11.3)	0.119
Hypertension (%)	68 (62.4)	25 (65.8)	43 (60.6)	0.591
Diabetes (%)	12 (11)	8 (21.1)	4 (5.6)	0.014
Hypercholesterolemia (%)	45 (41.3)	17 (44.7)	28 (39.4)	0.592
Cardioembolic etiology (%)	51 (46.8)	15 (39.5)	36 (50.7)	0.292
Baseline NIHSS score	10 (6–18.5)	10.5 (7.0–19.25)	10 (6–18)	0.610
Prebolus glycemia (mg/dL)	107.57 ± 21.76	114.81 ± 20.96	103.70 ± 21	0.010
Insulin levels (mU/L)	7.47 ± 10.19	13.01 ± 15.76	4.50 ± 1.85	0.003
Leukocyte (×10 <sup>3</sup> /μL)	7.96 (6.23–9.09)	8.69 (7.04–9.56)	7.10 (5.76–8.73)	0.007
Platelet (×10 <sup>3</sup> /μL)	202 (164–234)	206 (175–236)	195 (162–230)	0.298
Admission systolic BP (mmHg)	147.81 ± 23.84	151.42 ± 20.26	145.88 ± 25.49	0.250
Admission diastolic BP (mmHg)	78.44 ± 14.03	80.60 ± 13.57	77.28 ± 14.22	0.240
ASPECTS	10 (9.25–10)	10 (9–10)	10 (9.75–10)	0.970

Data are mean ± SD, n (%), or median (interquartile range), as appropriate.

clot lysis associated with increasing tertiles of the population distribution HOMA index, with the lower tertile as the reference. Results of the regression analyses are expressed as ORs and their corresponding CIs. A probability value <0.05 was considered significant.

## RESULTS

### Descriptive analysis

We studied 109 consecutive acute ischemic stroke patients with a documented MCA occlusion and without the patient's hyperglycemia treated with intravenous tPA. Forty-seven (43.1%) of them were female, and mean age was 71.0 ± 11.3 years. Table 1 summarizes the distribution of demographic characteristics and baseline clinical variables in patients belonging to the HOMA-IR upper tertile subgroup and patients of remaining HOMA-IR tertiles. Univariate analysis showed that patients belonging to the HOMA-IR upper tertile had more frequently a history of diabetes ( $P = 0.014$ ), higher glycemia on admission ( $P = 0.01$ ), and higher leukocytes level ( $P = 0.007$ ). However, there were no significant differences in main prognostic baseline variables across groups, including age and clinical severity as assessed by NIHSS.

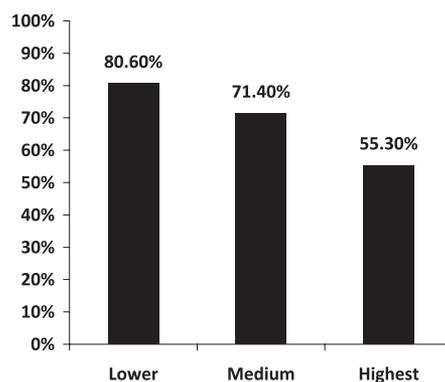
### IR and long-term outcome

Three months after stroke onset, six patients had died (mRS-score = 6) and we made a follow-up visit to all remaining

patients. Of them 34 (31.2%) had a mRS-score >2. HOMA-IR was higher in the poor outcome group (OR 1.66 [95% CI 1.08–2.73]) than in the group of patients with good outcome (1.29 [0.81–1.88];  $P = 0.02$ ). The probability of good clinical outcome decreased gradually with increasing HOMA-IR tertiles (Fig. 1).

When a logistic regression model adjusted by age, baseline NIHSS, baseline glycemia, and ASPECTS was applied, a HOMA-IR in the upper tertile was independently associated with poor outcome when compared with the lower tertile (OR 8.54 [95% CI 1.67–43.55];  $P = 0.01$ ), as shown on Table 2.

Bivariate analysis also identified the female sex ( $P = 0.026$ ), older age ( $P = 0.034$ ), history of diabetes ( $P = 0.005$ ),



**Figure 1—Relation between IR and long-term clinical outcome.** Bars show the probability of achieving good clinical outcome across HOMA-IR tertiles.

higher baseline NIHSS score ( $P < 0.001$ ), and platelet count ( $P = 0.049$ ) as significantly associated with long-term poor clinical outcome as represented in Table 3. After adjustment for those variables with  $P < 0.1$  on bivariate analysis, being in the upper HOMA-IR tertile remained as an independent predictor of poor outcome (adjusted OR 3.31 [95% CI 1.17–9.36];  $P = 0.024$ ). Other independent predictors of poor outcome were age and baseline stroke severity.

### Relationship between HOMA-IR and secondary end points

#### Symptomatic hemorrhagic transformation.

No relationship was found between HOMA-IR and symptomatic hemorrhagic transformation (sHT;  $P = 0.357$ ). No patients in the HOMA-IR lower tertile, 2 (5.7%) in the middle tertile, and 1 (2.8%) in the upper tertile developed sHT.

#### Resistance to intravenous thrombolysis.

Control TCD or TCCD to assess MCA status at 24 h was performed in 89 of 109 patients. Resistance to clot lysis was observed in 19 (21.3%) of them. HOMA-IR was significantly higher in those patients with persistent MCA occlusion 24 h after tPA bolus: OR 1.87 [95% CI 1.19–3.6] vs. 1.33 [0.8–2.00],  $P = 0.035$ . Having a HOMA-IR in the upper tertile level was associated with more persistent arterial occlusions after thrombolysis. The probability of resistance to clot lysis augmented gradually with increasing HOMA-IR tertiles (7% 1st tertile, 25% 2nd tertile, and 30% upper tertile).

Table 2—HOMA-IR tertiles and long-term clinical outcome

HOMA-IR tertiles	Poor outcome OR	P value
Tertile		
Lower: <1.03	Reference	
Middle: 1.03–1.71	2.96 [0.61–14.4]	0.178
Upper: >1.71	8.54 [1.67–43.35]	0.01

Data show age-, baseline NIHSS-, baseline glycemia-, and ASPECTS-adjusted odds ratio (OR) and 95% CI for poor long-term clinical outcome associated with increasing HOMA-IR tertiles, using the lower tertile as the reference.

A logistic regression analysis adjusted for age, baseline NIHSS, prebolus glycemia, and ASPECTS showed that having a HOMA-IR in the upper tertile, compared with the lower tertile, meant an eightfold increase in the probability of resistance to clot lysis 24 h after tPA infusion (adjusted OR 8.2 [95% CI 1.23–54.44];  $P = 0.029$ ).

**Infarct volume.** Patients in the upper IR tertile showed a clear trend toward higher final infarct volumes, although it did not reach statistical significance ( $48.1 \pm 83.4$  cubic centimeters in upper tertile vs.  $24.83 \pm 44.12$  cubic centimeters in the rest of tertiles;  $P = 0.061$ ).

**CONCLUSIONS**—In our previous works, we found metabolic syndrome to be associated with a higher resistance to intravenous thrombolysis for acute ischemic stroke (5,6). As a potential explanation for this observation, we hypothesized that the prothrombotic metabolic alterations related to IR, such as the derangement in

endogenous fibrinolysis, could be mediating this effect. However, in those studies we approached IR relying only on the clinical definition of metabolic syndrome, and no direct measure of IR was performed. Thus, the current study was designed to test this hypothesis more solidly using the HOMA-IR to directly quantify IR, which is known to provide a useful model to assess IR and  $\beta$ -cell function in epidemiological studies (16). In our new series of prospectively selected consecutive acute MCA ischemic stroke patients treated with intravenous thrombolysis, a higher IR was associated with a worse long-term functional outcome and with more lasting MCA occlusions, this association being independent of baseline clinical severity and glycemia.

Previous studies in acute ischemic stroke patients treated with intravenous thrombolysis have stressed the importance of achieving arterial recanalization as soon as possible in to improve clinical outcome

(17). In this context, IR could antagonize the effect of systemic thrombolysis by several potential mechanisms. First, patients with higher IR have elevated blood level of fibrinolysis inhibitors, such as plasminogen activator inhibitor 1, which may reflect an impairment of endogenous fibrinolytic capacity (18). Second, IR may affect the structure of the offending clot itself, rendering the clot more dense and resistant to lysis. Ex vivo studies in human clots have shown that the density of the clot augments with the increasing number of components of the metabolic syndrome (19). Moreover, the clots obtained from patients with metabolic syndrome are composed of thicker fibers and have more prolonged lysis times than the ones from individuals without increased IR (20). Third, IR may promote various conditions that could contribute to worsen the response to intravenous thrombolysis and stroke outcome in general, such as increased platelet activation, endothelial dysfunction, and a chronic proinflammatory state, among others (3). As an important practical implication of our findings, acute ischemic stroke patients with higher IR may be bad responders to intravenous thrombolysis and could benefit from more aggressive reperfusion approaches such as direct or rescue neuro-interventional procedures.

The results of our study support the notion that IR itself, independently of glycemia, may exert a deleterious effect in acute ischemic stroke. Indeed, hyperglycemia is known to be a strong determinant of poor stroke outcome in patients treated with intravenous thrombolysis by several putative mechanisms (21). To avoid the confounding influence of glycemia, patients presenting with acute hyperglycemia were excluded from our study. Despite having excluded hyperglycemic patients, IR still emerged as an independent predictor of a worse response to thrombolysis after adjustment for baseline glycemia in logistic regression models. In agreement with this finding, it has been shown in healthy humans that hyperinsulinemia may cause a selective impairment of fibrinolysis independent of glucose level (22).

This study has some limitations. First, the final sample was a small size, although highly selected, and therefore our results would need to be confirmed in a validation sample. Second, we used the HOMA-IR to quantify IR and not the gold standard hyperinsulinemic-euglycemic clamp because of practical limitations derived from our clinical setting. However, our selected method has been shown to correlate

Table 3—Results of the bivariate analysis of variables associated with poor long-term clinical outcome

Variables	Good outcome at 3 months (n = 75)	Poor outcome at 3 months (n = 34)	P value
Sex, female (%)	27 (36)	20 (55.8)	0.026
Age (years)	69.46 $\pm$ 11.4	74.41 $\pm$ 10	0.034
Smoking (%)	19 (25.3)	9 (26.5)	0.900
Alcohol (%)	7 (9.3)	2 (5.9)	0.544
Hypertension (%)	46 (61.3)	22 (64.7)	0.736
Diabetes (%)	4 (5.3)	8 (23.5)	0.005
Hypercholesterolemia (%)	32 (42.7)	13 (38.2)	0.663
Cardioembolic etiology (%)	33 (44)	18 (52.9)	0.443
Baseline NIHSS score	9.81 (5–13)	19 (12.50–22)	<0.001
Prebolus glycemia (mg/dL)	105.14 $\pm$ 21.99	112.94 $\pm$ 20.56	0.083
HOMA-IR	1.29 (0.81–1.88)	1.66 (1.08–2.73)	0.02
Leukocyte ( $\times 10^3/\mu\text{L}$ )	7.52 (6.22–8.76)	8.60 (6.45–10.26)	0.680
Platelet ( $\times 10^3/\mu\text{L}$ )	193 (162–232)	214 (191–257)	0.049
Admission systolic BP (mmHg)	145.46 $\pm$ 24.13	153.0 $\pm$ 22.7	0.127
Admission diastolic BP (mmHg)	78.74 $\pm$ 13.30	77.76 $\pm$ 15.70	0.737
Admission temperature ( $^{\circ}\text{C}$ )	35.74 $\pm$ 0.60	35.71 $\pm$ 0.59	0.858
ASPECTS	10 (10–10)	10 (8.5–10)	0.267

Data are mean  $\pm$  SD, n (%), or median (interquartile range), as appropriate. Results of multivariate analysis are shown in text.

reasonably well with clamp-derived values (14). Third, fasting blood samples used to determine HOMA-IR were obtained during the first 24 to 48 h after stroke onset and only once. We had to assume that HOMA-IR measured during admission in acute stroke patients may reflect differences in their prestroke IR status, since quantification of prestroke IR was not available. We cannot completely rule out that our values are affected by acute phase response and are therefore less valid as an estimate of prestroke IR. Nevertheless, our mean HOMA-IR values are comparable or even somewhat lower than the ones reported in the chronic phase after stroke, which argues against a substantial influence of acute phase reaction in our results (23).

In conclusion, high IR is associated with a worse response to intravenous thrombolysis in acute MCA ischemic stroke. IR may lead to a derangement of endogenous fibrinolysis, increased clot density, and prolonged lysis times as reflected by more persistent arterial occlusions, thus becoming a promising therapeutic target.

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