Plasma Adiponectin Levels and Five-Year Survival After First-Ever Ischemic Stroke

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Background and Purpose—This study aimed to investigate the association between plasma adiponectin levels and 5-year survival after first-ever ischemic stroke.

Methods—Plasma adiponectin measured within 24 hours after first-ever ischemic stroke was related to 5-year outcome. The Kaplan–Meier technique was applied in survival analysis, and the Cox proportional hazards model was used to evaluate the relationship between risk factors and prognosis.

Results—The probabilities of death were 92.8%, 52.5%, and 10.5% (P<0.001) for patients stratified according to tertiles of adiponectin (<4 μg/mL, 4 to 7 μg/mL, and >7 μg/mL, respectively). The relative risk of death was 8.1 (95% CI, 3.1, 24.5; P<0.001) for individuals with adiponectin levels in the lowest tertile compared with the upper tertile. Adiponectin <4 μg/mL (hazard ratio [HR], 5.2; 95% CI, 2.1, 18.4; P<0.001), score >15 in the National Institutes of Health Stroke Scale (HR, 3.6; 95% CI, 1.7, 15.9; P<0.001), and coronary heart disease (HR, 2.9; 95% CI, 1.5, 12.3; P<0.001) were independently associated with mortality.

Conclusions—Low plasma adiponectin is related to an increased risk of 5-year mortality after first-ever ischemic stroke, independently of other adverse predictors. (Stroke. 2005;36:1915-1920.)

Key Words: prognosis ■ stroke, ischemic ■ survival

Adiponectin (ADPN) is a recently discovered adipocytokine, structurally homologous with collagen VIII and X as well as with complement factor C1q. It is predominantly secreted by adipocytes and accounts for ~0.05% of total serum proteins. This novel molecule is found in higher levels among women than men and has been implicated in the development of atherosclerotic cardiovascular (CV) disease.

The levels of the ADPN are reduced in patients with obesity, insulin resistance, type 2 diabetes, hypertension, and coronary artery disease. Moreover, low plasma ADPN concentrations have been associated with greater risk of type 2 diabetes, myocardial infarction in men, as well as of CV events in patients with end-stage renal disease. In addition, data from animal and human studies suggest that this adipocytokine has insulin-sensitizing, antiatherogenic, and antiinflammatory properties.

Inflammatory processes play a fundamental role in atherosclerotic cerebrovascular disease and stroke, which is the second leading cause of death worldwide and a major cause of long-term disability. Only scant information exists so far on the relationship between ADPN and future stroke, whereas data on the prognostic significance of this protein in patients who already had a stroke are lacking. The aim of the present study was to investigate the association between ADPN levels and 5-year survival after first-ever ischemic stroke.

Materials and Methods

Baseline Assessment and Follow-Up
All subjects admitted between May 1998 and December 1999 with a presumable diagnosis of first-ever ischemic stroke were prospectively evaluated for inclusion in the study. Informed consent was obtained from all subjects or their legal representatives, and the study protocol was approved by our institutional committee. Cerebral infarction was defined as a focal neurological deficit of sudden onset that persisted for >24 hours in surviving patients, documented by brain computed tomography (CT) performed within the first 72 hours. Excluded were patients with concurrent renal or hepatic insufficiency, malignancy and recent infection, surgery, or major trauma. Initial stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS). The largest diameter (A) of the infarct and its largest perpendicular diameter (B) were measured with a caliper, whereas the third, vertical diameter (C) was determined by summing the thicknesses of the CT slices in which the lesion was visible. Infarct volume was calculated according to the formula 0.5×A×B×C, as described previously. CV death included (1) sudden death; (2) death from myocardial infarction, congestive heart failure, new fatal stroke, systemic or pulmonary

See Editorial Comment, pg 1919

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embolism, or peripheral arterial disease; and (3) death as consequence of the qualifying stroke in the absence of other intervening causes. Participants were prospectively assessed at 3, 6, and 12 months and subsequently every year until death or completion of 5 years after index stroke. Follow-up data were also obtained from physicians in private practice, hospital records, death certificates, and autopsy reports.

**Measurements**

Within 24 hours from stroke onset, fasting plasma samples were obtained and were stored at −80°C for subsequent assay. The plasma concentration of ADPN was evaluated by a commercially available sandwich ELISA (human ADPN ELISA; BioVendor Laboratory Medicine, Inc.) with a detection limit of 0.2 μg/mL and intra-assay and interassay coefficients of variation 6.4% and 7.3%, respectively. Continuous non-normally distributed variables were analyzed separately by using (1) a log-transformed normality distribution was assessed by the Kolmogorov-Smirnov test. Com-

Statistical Analysis

Analysis was performed using the Statistical Package for the Social Sciences software (SPSS Inc; release 10.0). The normality of data distribution was assessed by the Kolmogorov-Smirnov test. Comparisons were made by using (1) a χ2 test with Yates’ correction or Fischer exact test for categorical data, (2) unpaired Student t test or 1-way ANOVA for continuous normally distributed variables, and (3) the Mann–Whitney test or Kruskal–Wallis test as appropriate for continuous non-normally distributed variables. The k statistic was used to assess the level of agreement in the classification of subjects according to ADPN levels during the acute stroke phase and 1 year after stroke. The Kaplan–Meier technique was applied to survival analysis, and the log-rank test was used to compare rates of death. Significant univariate correlates were assessed in a multivariate Cox proportional hazards model. Ninety-five percent CIs were calculated for each comparison. All tests of significance were 2-tailed, and a P value <0.05 was used to indicate statistical significance.

**Results**

Among 164 patients diagnosed with first-ever ischemic stroke and fulfilling the inclusion criteria, adequate data on admission and follow-up were available for 160 individuals (97.6%) who were finally included in the analysis. Table 1 summarizes baseline demographic data, CV risk factors, and stroke characteristics of study participants. Patients were stratified into 3 groups according to tertile cutoff points (4 and 7 μg/mL) of the distribution of ADPN concentrations in the total study population.

Although no difference was detected in the percent of individual risks, there was a marginally significant negative correlation between ADPN levels and the number of stroke risk factors a patient had in this study (median 4 [range 2 to 7] factors; r = −0.32; P = 0.037), whereas all patients dying after the first year had ≥2 risk factors (median 3 [range 2 to 5] factors). The application of age-adjusted partial correlation coefficients yielded a marginally significant inverse correlation between ADPN and body mass index (BMI; r = −0.31; P = 0.033), hypertension (r = −0.28; P = 0.038), and diabetes mellitus (r = −0.25; P = 0.041), whereas there was no significant association with hypercholesterolemia (r = −0.13; P = 0.177), coronary heart disease (r = −0.11; P = 0.196), and peripheral arterial disease (r = −0.08; P = 0.224). NIHSS

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of the Study Population Consisting of Patients With First-Ever Ischemic Stroke</th>
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<tbody>
<tr>
<td>Characteristics, No. (%)</td>
</tr>
<tr>
<td>Demographic/anthropometric data</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Males (%)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>Cardiovascular risk factors/disease</td>
</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Hypercholesterolemia</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
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<tr>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td>Smoking (%)</td>
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<tr>
<td>Alcohol consumption, g/day of ethanol</td>
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<tr>
<td>Adiponectin levels, μg/mL</td>
</tr>
<tr>
<td>Stroke severity/types</td>
</tr>
<tr>
<td>NIHSS score, median (range)</td>
</tr>
<tr>
<td>Atherothrombotic</td>
</tr>
<tr>
<td>Cardioembolic</td>
</tr>
<tr>
<td>Lacunar</td>
</tr>
<tr>
<td>Treatment during hospitalization</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>Clopidogrel/ticlopidine</td>
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<tr>
<td>Warfarin</td>
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</tbody>
</table>

All differences between subgroups stratified according to adiponectin tertiles are nonsignificant.
score on admission and ADPN values had an inverse association (r = −0.20; P < 0.066), which also reached statistical significance only after adjustment for age (r = −0.29; P = 0.035). Initial infarct volume was precisely measured in 102 subjects (median 39.0 cm³ [interquartile range 9.0 to 93.0 cm³]) and was also found to have a consistent reciprocal correlation to ADPN levels with (r = −0.51; P = 0.002) and without adjustment for age (r = −0.41; P = 0.021). The value of CRP in the first 24 hours after stroke onset, which was available for 87 of the study participants (median 14 [range 2 to 41] mg/L), showed a significant negative correlation with ADPN as well (r = −0.48; P = 0.004).

Eighty-five patients (53.1%) died within 5 years after index stroke (66 [77.6%] because of CV events). About one third (29 of 85; 34.1%) and half (47 of 85; 55.3%) of total deaths occurred within the first 30 days and the first year after stroke, respectively. The overall 30-day and 1-year case fatality rates were 18.1% (29 of 160) and 29.4% (47 of 160), respectively, whereas after the first year, ∼10% of survivors continued to die each year (8.9%, 8.7%, 10.6%, and 10.7% from second to fifth year). Subjects who died during the 5-year follow-up period had lower mean ADPN (4.1 ± 2.1 μg/mL) than survivors (7.3 ± 2.2 μg/mL; P < 0.001). Nonfatal CV events were observed in 27 of 160 participants during the 5 years (16.9%; 13 events within the first year), being as well more common in subjects with ADPN <4 μg/mL (13 of 42; 31%) than 4 to 7 μg/mL (12 of 80; 15%) or >7 μg/mL (2 of 38; 5.3%; P < 0.001).

A greater probability of CV (80.9%) and all-cause 5-year mortality (92.8%) was found in patients with ADPN in the lowest tertile compared with the middle (37.5% and 52.5%, respectively) and the upper tertile (5.2% and 10.5%, respectively; P < 0.001) (Figure). Similar associations existed with regard to the 30-day and the 1-year probability of death, both being greater in patients with ADPN concentrations <4 μg/mL (P < 0.05 and P < 0.01, respectively). Compared with individuals with ADPN in the highest tertile, the relative risk of death within 5 years was 8.1 (95% CI, 3.1, 24.5; P < 0.001) for subjects with ADPN in the lowest tertile and 4.3 (95% CI, 1.5, 14.6; P < 0.01) for those with ADPN in the middle tertile.

Additional measurements of ADPN and CRP were performed 1 year after index stroke in 71 of the 113 1-year survivors who were considered as lacking other conditions that could influence the levels of the latter proteins. Using data only from the >71 patients with acute phase and 1-year values, ADPN 1 year after stroke (mean ± SD; 7.8 ± 2.5 μg/mL) did not differ significantly from the initial average value (7.3 ± 1.6 μg/mL; P = 0.102), whereas the 2 measurements were highly correlated (r = 0.84; P < 0.001), the above associations persisting after adjustments for BMI. Not only the 1-year follow-up ADPN levels were similar to the initial ones, but also the majority of the above patients (66 of 71; 93%) tended to be in the same ADPN tertile groups as initially stratified (κ = 0.89; P < 0.001). CRP of the >71 subjects declined significantly within 1 year (median 1-year value 6 [range 1 to 13] mg/L compared with 9 [range 1 to 21] mg/L in the acute stroke phase; P = 0.019) but still remained higher than the upper normal limit of 5 mg/L. Nevertheless, CRP at 1 year after the event showed a significant positive correlation with its baseline values (r = 0.45; P = 0.011) as well as a negative correlation with ADPN at 1 year (r = −0.41; P = 0.017).

Univariate correlates of mortality within 5 years were initial NIHSS score (odds ratio [OR], 4.9; 95% CI, 2.1, 11.2; P < 0.001), ADPN levels (OR, 3.8; 95% CI, 1.6, 9.1; P < 0.001), coronary heart disease (OR, 3.3; 95% CI, 1.5, 8.4; P < 0.01), age >70 years (OR, 3.1; 95% CI, 1.4, 7.7; P < 0.05), and peripheral arterial disease (OR, 2.7; 95% CI, 1.2, 6.5; P < 0.05). In the multivariate Cox model, the risk of death was significantly associated with an ADPN level in the lowest tertile, stroke severity on NIHSS, and coronary heart disease (Table 2).

**Discussion**

The present study suggests that low ADPN levels appear to be associated with poor outcome after first-ever ischemic stroke independently of other adverse predictors. Further, the

### TABLE 2. Independent Predictors of Mortality in the Total Study Population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subjects With the Variable (% of the overall population)</th>
<th>Deaths Within 5 y (% of subjects with the variable)</th>
<th>P Value</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin &lt;4 μg/mL</td>
<td>42 (26.3)</td>
<td>39 (92.8)</td>
<td>&lt;0.001</td>
<td>5.2</td>
<td>2.1, 18.4</td>
</tr>
<tr>
<td>NIHSS score &gt;15</td>
<td>76 (47.5)</td>
<td>57 (75)</td>
<td>&lt;0.001</td>
<td>3.6</td>
<td>1.7, 15.9</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>61 (38.1)</td>
<td>43 (70.5)</td>
<td>&lt;0.001</td>
<td>2.9</td>
<td>1.5, 12.3</td>
</tr>
</tbody>
</table>
reciprocal relationship between initial infarct volume and ADPN in a subgroup of our stroke population outlines the potential role of the latter protein as a biomarker inversely reflecting the extent of brain injury. These results are consistent with previous reports indicating that an excessive inflammatory response in coronary and cerebral arteries may be related to scantiness of this adipocytokine, which could be considered an endogenous biological modulator of vascular remodeling.

The intriguing finding of no inverse relationship between CV risk factors and ADPN in our study (Table 1) might be attributed to several reasons. First, an acute phase reaction could blur the above association, inasmuch as our investigation is the first to assess ADPN in the first day after the onset of a CV event. In this respect, ADPN was shown to have a significant negative correlation with CRP in a subgroup of the present study participants. Second, a confounding influence of age on the results could not be excluded because we evaluated an older population than most of the previous studies. Although the elderly could be anticipated to have lower ADPN levels given the increased prevalence of CV risk factors, a positive correlation between ADPN and age has repeatedly been demonstrated. It has been suggested that aging and advanced stages of CV disease may trigger a counter-regulatory response that raises plasma ADPN, thus inverting to some extent its original association with CV risk factors. In line with the latter hypothesis is the marginally significant reciprocal association of ADPN with BMI, hypertension, and diabetes mellitus, which was revealed in the present study after adjustment for age. Third, the possibility of a type 2 statistical error could not be ruled out, taking into account the relatively limited sample size of 2 of the 3 groups stratified according to ADPN levels.

Whereas the value of plasma ADPN shows a wide variation in humans (1 to 30 μg/mL), apparently healthy individuals usually have ADPN ranging from 6 to 20 μg/mL, the latter thresholds suggested as defining “normal” ADPN levels. Thus, the mean ADPN value (6.1 μg/mL) in our population of patients in the poststroke acute phase could be classified at the low cutoff of “normal” interval. Nevertheless, few data exist on the expected poststroke ADPN levels in subjects with risk factors, derived from a Nested case-referent study that showed no predictive value of this adipocytokine for future stroke. In the latter study, the mean ADPN concentration of 276 subjects who subsequently developed stroke (11.5 μg/mL in men and 18.2 μg/mL in women) did not differ from that observed in the corresponding referents. Furthermore, albeit a single assessment of ADPN may be susceptible to short-term variation that would be a possible source of misclassification, the strong correlation of ADPN concentrations measured 1 year after stroke with the initial values in a subgroup of the present population corroborates the results of a previous study showing intraindividual ADPN levels to be stable over time. The above observation implies that low poststroke ADPN may not be linked only to an immediate, acute process related to stroke but also to a persistent inflammatory response in stroke survivors as suggested previously.

Our results may boost the scientific rationale for considerable therapeutic implications. Weight reduction by surgery or by lifestyle modifications, as well as treatment with thiazolidinediones, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers have been reported to increase plasma ADPN. Nevertheless, conflicting data exist so far on the impact of administration of statins on ADPN levels because treatment with atorvastatin did not alter ADPN in a trial on subjects who had diabetes or were at high risk for developing diabetes, whereas the combination of simvastatin with rosuvastatin increased ADPN in a very recent study on hypercholesterolemic hypertensive patients.

The present study provides additional support to the view that there is an adipovascular axis with ADPN representing a direct link between insulin resistance, obesity, and atherosclerosis. Therefore, it is a challenge for interventional trials to target this protein as a surrogate end point to investigate whether increasing ADPN levels by weight reduction or drug administration may prolong survival of stroke patients.

References
Adiponectin Spectator or Player?

Despite efforts at controlling traditional risk factors, stroke remains a devastating and all-too-common disease. Identifying new markers for patients at higher risk of stroke would aid in future risk factor management as well as potentially offering new venues for preventive therapies. In this issue of Stroke, Efthathiou et al report on a highly significant inverse relation between adiponectin levels and subsequent 5-year mortality. Adiponectin, a recently discovered cytokine, has previously been theorized to be involved in the development of atherosclerotic disease. Adiponectin appears to have both anti-inflammatory and antiatherogenic properties, and as such, it was expected that there would be an inverse relation between the serum level of adiponectin and subsequent cerebrovascular mortality. In their study, Efthathiou et al confirm this inverse relation, finding that patients with adiponectin levels in the lowest tertile had a 92.8% 5-year mortality compared with a 10.5% mortality in patients with adiponectin levels in the highest tertile. This corresponds to an 8-fold increase in risk for individuals with low adiponectin levels compared with those with the highest tertile of adiponectin levels. Similar results with adiponectin have been seen in cardiovascular disease. In a case-control analysis from the Health Professionals Follow-up Study, among the 18,225 men without cardiovascular disease at baseline, those in the highest quintile of adiponectin level had a significantly reduced risk for myocardial infarction (relative risk [RR], 0.39; 95% confidence interval, 0.23 to 0.64; P for trend <0.001) compared with in the lowest quintile of adiponectin level.

The results of this study support the role of cytokines in stroke and are consistent with prior studies suggesting that a persistent inflammatory response increases the risk of subsequent cerebrovascular disease. The first group to demonstrate a persistent inflammatory response was Beamer et al, who found that fibrinogen, C-reactive protein (CRP), and white blood cell levels at baseline were predictive of recurrent vascular events at 1 year. They also found that fibrinogen, C-reactive protein, and white blood cell levels at baseline were predictive of recurrent vascular events at 1 year. They also found that fibrinogen, C-reactive protein, and white blood cell levels at baseline remained significantly elevated at 1 year and that it continued to predict an increased risk for recurrent vascular events. However, the magnitude of the ability of fibrinogen to predict recurrent events was much less than that seen in the current adiponectin study. Other markers of the inflammatory response, including interleukin (IL)-6 and CRP, did not independently predict recurrent events in their study.

In addition to fibrinogen, some of the other inflammatory markers that have been linked to recurrent cardiac or stroke events include CRP, IL-6, and cell adhesion

Editorial Comment

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molecules such as soluble intercellular adhesion molecule-1 (RR, 3).9 These compare to the 8-fold increased RR seen in the current study. However, it should be noted that all of these results were based on studies involving thousands of patients compared with the 160 studied by Efstathiou et al.

The current study found that apidonectin levels were low-normal after acute stroke. Prior studies found that the anti-inflammatory cytokines IL-6 and IL-1RA increase acutely after stroke,10 implying that there is activation of anti-inflammatory components. The finding that apidonectin did not increase acutely suggests that although apidonectin may be protective, there may be no mechanisms to quickly upregulate it, at least shortly after stroke.

In the current study, apidonectin appears to be both potentially a marker of the extent of underlying neurologic injury and a marker of persistent inflammatory response. That apidonectin is in part a marker for the extent of neurologic injury is supported by the negative correlation between initial infarct volume and apidonectin, as well as the inverse relation between the National Institutes of Health Stroke Scale and apidonectin levels. However, the authors also provide data supporting the theory that apidonectin is involved in a chronic anti-inflammatory response; in the 71 patients tested at 1 year, apidonectin levels remained nearly the same as they had at baseline. In addition, patients tended to be in the same apidonectin tertile group to which they were initially stratified. The authors also found a significant negative correlation with apidonectin and CRP (P=0.004); however, they did not provide information as to whether CRP was as powerful a predictor of 5-year mortality as the apidonectin level was. In addition, although CRP remained elevated compared with normal in the 71 patients assessed at 1 year, it was more likely to have declined from the initial baseline value compared with an apidonectin level that had shown very little change from baseline. This suggests that CRP is relatively more reflective of an acute-phase reaction, whereas apidonectin is more representative of the underlying chronic inflammatory state of the patient.

What this article does not tell us is whether apidonectin is merely a marker of a persistent inflammatory response or whether it has anti-inflammatory properties. There are some limited data that apidonectin may have some direct insulin-sensitizing and anti-inflammatory properties.2 The only way of proving this in cerebrovascular cases would be to design a therapeutic trial that targets elevating apidonectin levels in patients at risk for stroke. The first step in designing such a therapeutic trial would be to discover an agent that reliably elevates apidonectin levels. In the discussion section, the authors reviewed several medications that have variable effects on raising apidonectin levels. It appears that further work confirming an effective apidonectin-elevating therapy is indicated.

The results of this study support the theory that inflammation is involved in recurrent stroke and mortality. At the very least, apidonectin appears to be a robust marker of subsequent vascular events. However, it could also provide fertile ground for potential therapeutic trials that target increasing apidonectin.

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References

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