Elevated Levels of Hemoglobin A1c Are Associated With Cerebral White Matter Disease in Patients With Stroke

Michal Rozanski, MD; Tobias B. Richter; Ulrike Grittner, PhD; Matthias Endres, MD; Jochen B. Fiebach, MD; Gerhard J. Jungehulsing, MD

**Background and Purpose**—This study was conducted to investigate the association of cerebral white matter disease (WMD) on MRI with vascular risk factors and laboratory findings in consecutive first acute ischemic stroke patients.

**Methods**—Acute ischemic stroke patients underwent MRI ≤24 hours after stroke onset and follow-up on day 2. WMD was scored on fluid attenuated inversion recovery MRI according to the Wahlund score. Vascular risk factors and laboratory parameters were assessed during hospital stay. Univariate and multiple logistic regression analyses were performed.

**Results**—We included 512 patients with first acute ischemic stroke (mean age, 68.5 [SD, 13.2] years; 192 women (37.5%); median National Institutes of Health Stroke Scale on admission, 3 [interquartile range, 1–6]; and median Wahlund score, 4 [interquartile range, 2–9]). WMD was present in 460 (89.8%) patients. In univariate analysis, age, arterial hypertension, reduced estimated glomerular filtration rate, hemoglobin A1c (HbA1c) levels, diabetes mellitus, and female sex were associated with the presence of WMD (P<0.05). In multiple regression analysis, age, arterial hypertension, and elevated levels of HbA1c (P<0.05) remained independently associated with the extent of WMD.

**Conclusions**—Among known risk factors, higher levels of HbA1c were associated with cerebral WMD in stroke patients. This may suggest that chronic disturbance of glycemia measured by HbA1c plays a role in the pathophysiology of WMD.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00715533. (Stroke. 2014;45:00-00.)

**Key Words:** ischemia ▪ leukencephalopathies ▪ magnetic resonance imaging

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Cerebral white matter disease (WMD) is detected by hyperintense changes on T2 or fluid attenuated inversion recovery MRI. Histologically, these hyperintensities correlate with spongiosis, gliosis, and patchy demyelination in white matter and are typically caused by ischemia. WMD has gained growing interest, because it may play a role in cognitive decline and as a risk factor for first and recurrent ischemic stroke and death.

The pathophysiology of WMD is not completely understood, and several etiologic mechanisms are discussed. The majority of research and experimental findings suggest chronic ischemic pathogenesis in the development and progression of WMD. Factors consequently found to be associated with WMD were age and arterial hypertension (HTN). The influence of other vascular risk factors such as diabetes mellitus (DM), dyslipidemia, smoking, and renal function remains controversial, because the results of available studies are contradictory. DM type 1 was shown to be a strong risk factor for WMD among young stroke patients. Although there are studies that confirm the association between DM and WMD in the general population, 2 of these were conducted in small cohorts. Metabolic syndrome has been shown to be significantly associated with WMD, but DM prevalence was not analyzed by the authors in this study. In contrast to these findings, a large study showed progress of brain atrophy, but not WMD, in patients with DM. Furthermore, there was no significant association between DM and WMD in studies including >2000 participants after adjustment for confounders. Hemoglobin A1c (HbA1c), a biomarker of long-term glycemic control, was not taken into consideration in the aforementioned studies. Few studies conducted in small prespecified cohorts have suggested significant association between levels of HbA1c and WMD. However, these observations were not confirmed when a larger cohort of stroke patients was assessed. The role of renal function in WMD was shown in young stroke patients. In studies on the general population, these results have only partially been replicated.

Stroke is considered a risk factor for WMD and vice versa, that is, WMD predisposes for stroke; therefore, we think that patients with stroke should be thoroughly examined.
of the possible impact of glycemic disturbances and renal dysfunction reflected by easily controlled parameters might help in the prevention of WMD.

Methods

Study Population

The study population derives from a large prospective stroke MRI study (NCT00715533) approved by the local ethics committee of Charité, Universitätmedizin Berlin.29 Each patient gave written informed consent. Consecutive patients admitted between May 2008 and October 2011 in the Department of Neurology, Charité, Universitätmedizin Berlin, Campus Benjamin Franklin, with suspected AIS were screened. Patients were considered eligible for further analysis if MRI was completed <24 hours after stroke onset and past medical history could be obtained. All patients provided serum samples on hospital admission and day 2. Clinical and sociodemographical data, National Institutes of Health Stroke Scale scores, and modified Rankin Scale scores, as well as data on vascular risk factors (DM, HTN, atrial fibrillation, hypercholesterinemia, and current smoking), were collected. The stroke subtype was categorized for every patient using Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.30

Imaging

All patients underwent a standard 3T (Tim Trio; Siemens AG, Erlangen, Germany) stroke MRI protocol as described elsewhere.29 In brief, the protocol consisted of T2*, diffusion-weighted imaging, time-of-flight MR angiography, fluid attenuated inversion recovery, and perfusion imaging. The extent of WMD was analyzed on fluid attenuated inversion recovery using the Wahlund visual rating score (WS) by neurologists experienced in MRI and stroke, blinded to demographics and risk factors (M.R. and G.J.J.).31 In cases of rater disagreement, MRI was discussed with a neuroradiologist (J.B.F.). Patients with WMD were divided into 4 groups depending on WS—0 (no white matter lesions), 1 to 4, 5 to 9, and >9 lesions.32 The assessment of imaging data was performed blinded to clinical and laboratory findings.

Assessment and Analysis of Laboratory Findings

Blood samples including creatinine, electrolytes, erythrocytes (RBC), and leukocytes were drawn on admission. On day 2, fasting serum samples were collected and high-density lipoprotein, low-density lipoprotein, triglycerides, cholesterol, and Hba1c assessed. All measurements were performed in the laboratory of Charité Hospital in Berlin according to international standards. eGFR was calculated using creatinine clearance in the 4-variable Modification of Diet in Renal Disease equation: eGFR=186×Scr^{−1.154}×age^{−0.203}×1.210 (if black) and ×0.742 (if woman).33

Statistical Analysis

First, we analyzed the associations of sociodemographics, risk factors, laboratory findings, and imaging scores with the 4 WMD groups based on WS (0; 1–4; 5–9; >9) in univariate analyses using ordinal logistic regression models with WS group as a dependent variable. Second, for significant associations, we tested whether, after adjustment for age, the association still remained. In the next step, a multiple ordinal logistic regression model was used to identify factors that are independently and significantly associated with the extent of WMD. P values <0.05 were considered statistically significant. No correction for multiple testing was performed. We used a stepwise backward procedure. Additionally, we tested a model where we forced DM and other confounders. All statistical analyses were performed using IBM SPSS Statistics version 19.0.0.1 (SPSS, Inc, IBM Company, Chicago, IL).

Results

We screened a total of 755 patients (mean age, 68.1 [SD, 13.9] years; 291 women) with suspected ischemic stroke <24 hours of symptom onset. We excluded 71 patients because of a clinical diagnosis other than ischemic stroke, 45 who were diagnosed with transient ischemic attacks, 122 with recurrent stroke, and 5 patients with incomplete MRI sequences. Hence, statistical analyses were conducted in 512 patients (mean age, 68.5 [SD, 13.2] years; 192 (37.5%) women; median National Institutes of Health Stroke Scale score on admission, 3 [interquartile range, 1–6], median WS, 4 [interquartile range, 2–9]). According to TOAST classification, in 117 (22.9%) patients, the cause of stroke was large artery atherosclerosis, in 125 (24.4%) cardioembolism, in 56 (10.9%) small artery occlusion (lacune), in 14 (2.7%) other determined cause, and in 200 (39.1%) undetermined cause.

Of all patients, 394 (77%) had HTN, 253 (49.5%) hypercholesterinemia, 124 (24.2%) atrial fibrillation, and 120 (23%) DM. Demographics, risk factors, frequency of stroke and WMD, and median levels of laboratory parameters according to WS are shown in Table 1. Examples of MRI with WMD are shown in Figure 1.

Univariate analyses revealed a significant association between WMD severity and age, female sex, HTN, and DM (P<0.05; Table 1). Higher Hba1c levels and lower eGFR were the only laboratory parameters significantly associated with WMD (P<0.001; Table 1). After age adjustment, the association between extent of WMD and female sex as well low eGFR was no longer significant.

In multiple ordinal logistic regression analyses, age, HTN, and higher levels of Hba1c remained significantly associated with the extent of WMD (P<0.05; Table 2, model with Hba1c). After additionally including DM, Hba1c was not significantly associated with the extent of WMD any more (P=0.087; Table 2, model with DM and Hba1c), but the goodness-of-fit parameter (~2 Log Likelihood) of both models (model with confounders and Hba1c, model with confounders Hba1c and DM) showed that the additional adjustment for DM did not improve the model. Figure 2 shows the distribution of Hba1c levels in different WMD severity groups.

Discussion

We investigated known and potential risk factors for WMD in a relative large consecutive population of patients with first AIS. Our results underline the high prevalence of WMD in elderly persons and in patients with a history of HTN.12,16 The most important result of our study is that elevated levels of Hba1c were associated with WMD lesion load. To the best of our knowledge, this is the first study showing the possible role of glycemic disturbance as a risk factor for WMD measured by Hba1c. Previous studies assessing the relationship between WMD and DM, metabolic syndrome, dyslipidemia, higher levels of fasting glucose, and increased insulin resistance yielded controversial results.11,12,14,16,17,22,23 In these studies, however, Hba1c was not analyzed. A similar study by Heo et al25 showed rather unexpected negative association between Hba1c and severe WMD in diabetic patients. The authors did not take into consideration DM in
In the study of Murray et al., HbA1c was associated with deep white matter hyperintensities. But this study had a relatively small sample size that was comprised primarily of elderly participants. Manschot et al. showed that brain atrophy and white matter changes in patients with DM might be responsible for cognitive decline and observed a modest association between HbA1c and white matter hyperintensities in a small cohort of patients with DM. In our study, DM was associated with WMD severity only in univariate analysis, but not in multiple regression analysis. Higher levels of HbA1c seemed to be stronger associated with WMD (−2 Log Likelihood, 1023.5 [df, 3]) compared with the diagnosed DM variable (−2 Log Likelihood: 1027.7 [df, 3], model not shown). This may be explained by the fact that patients with glycemic disturbances, such as prediabetes or impaired glucose regulation, may have HbA1c levels >5.7% but not yet diagnosed with DM according to guidelines. Conversely, patients with DM may have tightly controlled glucose levels and, therefore, HbA1c levels below 5.7%. For the majority of patients, higher levels of HbA1c are associated with DM.

### Table 1. Association of Demographics, Risk Factors, Laboratory Findings and Imaging Patterns, and the Extent of WMD

<table>
<thead>
<tr>
<th>Demographics</th>
<th>N Total</th>
<th>WS, 0 (n=52)</th>
<th>WS, 1–4 (n=205)</th>
<th>WS, 5–9 (n=139)</th>
<th>WS, &gt;9 (n=116)</th>
<th>P Value</th>
<th>Age-Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>512 68 (13)</td>
<td>52 (15)</td>
<td>65 (12)</td>
<td>73 (9)</td>
<td>76 (9)</td>
<td>&lt;0.001</td>
<td>0.361</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>512 320 (62.5)</td>
<td>38 (73.1)</td>
<td>137 (66.8)</td>
<td>89 (64.0)</td>
<td>56 (48.3)</td>
<td>0.001</td>
<td>0.012</td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>512 120 (23.4)</td>
<td>5 (9.6)</td>
<td>44 (21.5)</td>
<td>33 (23.7)</td>
<td>38 (32.8)</td>
<td>0.002</td>
<td>0.114</td>
</tr>
<tr>
<td>HTN</td>
<td>512 394 (77.0)</td>
<td>19 (36.5)</td>
<td>149 (72.7)</td>
<td>119 (85.6)</td>
<td>107 (92.2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>508 125 (24.4)</td>
<td>17 (32.7)</td>
<td>53 (25.9)</td>
<td>29 (20.9)</td>
<td>26 (22.4)</td>
<td>0.114</td>
<td></td>
</tr>
<tr>
<td>HCL</td>
<td>511 253 (49.6)</td>
<td>19 (37.3)</td>
<td>101 (49.3)</td>
<td>74 (53.2)</td>
<td>59 (50.8)</td>
<td>0.173</td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td>512 124 (24.2)</td>
<td>7 (13.5)</td>
<td>46 (22.4)</td>
<td>45 (32.4)</td>
<td>26 (22.4)</td>
<td>0.153</td>
<td></td>
</tr>
</tbody>
</table>

Laboratory, median (IQR)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (IQR)</th>
<th>WS, 0 (n=52)</th>
<th>WS, 1–4 (n=205)</th>
<th>WS, 5–9 (n=139)</th>
<th>WS, &gt;9 (n=116)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR MDRD, mL/min</td>
<td>505 76.5 (64.1–92.2)</td>
<td>83.7 (71.0–100.9)</td>
<td>79.8 (67.2–92.8)</td>
<td>73.7 (61.9–88.2)</td>
<td>70.6 (56.7–88.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>440 5.05 (4.38–5.78)</td>
<td>4.90 (4.43–5.46)</td>
<td>5.00 (4.20–5.78)</td>
<td>5.05 (4.20–5.91)</td>
<td>5.15 (4.56–5.93)</td>
<td>0.135</td>
</tr>
<tr>
<td>TG*, mmol/L</td>
<td>412 1.25 (0.98–1.77)</td>
<td>1.25 (0.91–1.40)</td>
<td>1.38 (1.01–1.89)</td>
<td>1.21 (0.98–1.61)</td>
<td>1.21 (0.99–1.71)</td>
<td>0.907</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>454 1.3 (1.1–1.6)</td>
<td>1.4 (1.1–1.7)</td>
<td>1.3 (1.0–1.5)</td>
<td>1.3 (1.1–1.6)</td>
<td>1.3 (1.1–1.5)</td>
<td>0.919</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>471 3.0 (2.4–3.7)</td>
<td>2.8 (2.3–3.1)</td>
<td>3.1 (2.5–3.7)</td>
<td>3.0 (2.4–3.8)</td>
<td>3.1 (2.5–3.8)</td>
<td>0.241</td>
</tr>
<tr>
<td>HbA1c*, %</td>
<td>459 5.8 (5.4–6.3)</td>
<td>5.3 (5.1–5.6)</td>
<td>5.7 (5.4–6.1)</td>
<td>5.8 (5.5–6.4)</td>
<td>5.9 (5.6–6.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Univariate analysis, adjusting for age (right column), and WMD extent divided into groups depending on Wahlund score. AF indicates atrial fibrillation; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HCL, hypercholesterinemia; HDL, high-density lipoprotein; HTN, arterial hypertension; IQR, interquartile range; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease; TG, triglycerides; WMD, white matter disease; and WS, Wahlund score.

*Log-transformed values were used in regression models.

### Table 2. Multiple Ordinal Regression of Factors Significantly Associated With WMD

<table>
<thead>
<tr>
<th>Variables</th>
<th>β</th>
<th>SE</th>
<th>P Value</th>
<th>β</th>
<th>SE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td>0.08</td>
<td>0.01</td>
<td>&lt;0.001</td>
<td>0.08</td>
<td>0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
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<tr>
<td>Risk factors</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>0.12</td>
<td>0.27</td>
<td>0.668</td>
</tr>
<tr>
<td>HTN</td>
<td>0.73</td>
<td>0.24</td>
<td>0.002</td>
<td>0.73</td>
<td>0.24</td>
<td>0.002</td>
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<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>eGFR</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>HbA1c*</td>
<td>4.00</td>
<td>1.34</td>
<td>0.003</td>
<td>3.52</td>
<td>1.75</td>
<td>0.087</td>
</tr>
<tr>
<td>Model fit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R² (Nagelkerke)</td>
<td>0.30</td>
<td></td>
<td></td>
<td>0.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>−2LL†</td>
<td>1023.5 (df, 3)</td>
<td></td>
<td></td>
<td>1027.7 (df, 4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†Likelihood ratio test for comparison of both models; P=0.041.

Figure 1. Cerebral white matter disease in 2 different patients, periventricularly and in basal ganglia (A) in the first example. White matter changes are localized periventricularly and in some extent subcortically in another patient (B).
Endothelial dysfunction in hyperglycemic states may also contribute to small vessel injury. \textsuperscript{37} The differences in levels of HbA1c ranges between patients without WMD (WS 0) and groups with any sign of WMD was statistically significant in multiple regression analysis (P=0.003).

As expected. Therefore, we calculated an additional regression model including DM as a risk factor and HbA1c. In this model, the association between HbA1c and extent of WMD is no longer significant (P=0.087), but the model fit did not improve after including DM (Table 2). Therefore, poor glycemic control, with even slight disturbances reflected by HbA1c, may also be a risk factor for WMD.\textsuperscript{22,23,35} Median levels of HbA1c in groups of patients with any sign of WMD were 5.7% to 5.9% versus 5.3% in patients without hyperintensities, and hence within the 5.7% to 6.5% range recommended by the American Diabetes Association to diagnose prediabetes or high risk for DM.\textsuperscript{34} HbA1c is used to approximate serum glucose levels over the past 3 months. It is an end product of nonenzymatic glycation and thus a surrogate marker of glycaemia. HbA1c presumably does not play a role in the development of microvascular changes in the brain.\textsuperscript{41} Whereas, hyperglycemia has been shown to lead to microinfarctions and white matter lesions indirectly.\textsuperscript{36} These processes could be explained by capillary thickening followed by narrowing of vessel lumen and subsequent chronic ischemia as found in the brains of patients with DM and WMD.\textsuperscript{1} Endothelial dysfunction in hyperglycemic states may also contribute to small vessel injury.\textsuperscript{37} The differences in levels of HbA1c were highly significant in our study but rather low, so that further investigations in larger cohorts are needed to explore the subgroup of patients with levels in the prediabetic range and confirm our findings before it could be used as a potential marker for increased WMD risk.

In our study, women had a higher prevalence and extent of WMD, but after adjusting for age, sex differences were no longer significant (Table 1) because of age differences between both sexes, 72 (SD, 14.5) years in women versus 66 (SD, 12) years in men (P<0.05; data not shown). We did not find a significant association between impaired kidney function and WMD after adjusting for age. One reason for this finding could be that our patient cohort was older than that in other studies.\textsuperscript{13,15} The link between age and both decreased kidney function and WMD severity is well established.\textsuperscript{38} The possible age-related GFR reduction in our cohort could have been understated by the higher age in our cohort. Moreover, the calculation of GFR using the Modification of Diet in Renal Disease formula could overestimate GFR in elderly patients.\textsuperscript{33} In general population studies, multiple regression models revealed an association between GFR and WMD but either only in patients with severe renal dysfunction or even loss of significance after controlling for risk factors, which is in accordance with our results.\textsuperscript{12,26,27} We did not find any significant association between levels of triglycerides, low-density lipoprotein, high-density lipoprotein, cholesterol, and WMD. This issue is being discussed by many authors, and its impact on WMD remains vague.\textsuperscript{12,14,16}

Our study has some limitations. The cross-sectional design of our study does not allow assessing factors influencing the development and progression of WMD. Such data should be analyzed in larger epidemiological, longitudinal studies. Our study population is homogenous, but because patients may be especially prone to developing more severe WMD after stroke, AIS patients may constitute a potential target group for more precise glycemic control.\textsuperscript{3,28} Although the parameters we analyzed are not novel, the few studies that have previously assessed them yielded conflicting results. Moreover, if WMD prevention can be optimized by monitoring simple laboratory values, it is warranted that these parameters be thoroughly investigated.

Conclusions

We demonstrated that WMD in patients with first AIS is associated with age, HTN, and higher levels of HbA1c. This may suggest that stroke patients with prediabetic levels of HbA1c or inadequate glycemic control measured by HbA1c are at risk for WMD. Further studies are needed to establish possible values of HbA1c as a potential marker for increased WMD risk.

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