Kidney Function and White Matter Disease in Young Stroke Patients
Analysis of the Stroke in Young Fabry Patients Study Population

Robert Steinicke, MD; Beate Gaertner, Dr rer med; Ulrike Grittker, Dr phil; Wolf Schmidt, MD; Martin Dichgans, MD, PhD; Peter U. Heuschmann, MD, MPH; Christian Tanislaw, MD; Jukka Putaala, MD, PhD; Manfred Kaps, MD; Matthias Endres, MD; Reinhold Schmidt, MD; Franz Fazekas, MD; Bo Norrving, MD; Arndt Rolfs, MD; Peter Martus, Dr rer nat; Turgut Tatlisumak, MD, PhD; Christian Enzinger, MD; Gerhard Jan Jungehulsing, MD

Background and Purpose—Impaired kidney function is thought to be associated with small vessel disease, outcome, and mortality in the general stroke population. Data are limited regarding young patients. The aim of this study was to investigate the association of kidney function and white matter hyperintensities (WMHs) in young patients with first ischemic stroke.

Methods—We analyzed 2500 young (18–55 years) patients with first-ever ischemic stroke from the prospective observational Stroke in Young Fabry Patients (SIFAP1) study with available MRI data on WMH. Of these, 2009 had available data concerning estimated glomerular filtration rate (eGFR). Kidney function was expressed as eGFR by the Modification of Diet in Renal Disease method. Deep WMHs on MRI were classified by the Fazekas score. Multivariate analysis was performed using a regression model with random effects.

Results—Mean eGFR was 96.7 mL/min in those with WMH Grade 0 to 1 (none to mild), 90.7 mL/min in WMH Grade 2 (moderate), and 89 mL/min in WMH Grade 3 (severe). Univariate analysis revealed WMH to be associated with age (P<0.001), hypertension (P<0.001), cardiovascular disease (P=0.015), overweight (body mass index >25 kg/m²; P=0.013), current smoking (P=0.044), and eGFR (P=0.009). In multivariate analysis, age, hypertension, and eGFR remained associated with WMH severity.

Conclusions—In young patients with acute ischemic stroke, lower eGFR values in the normal range are associated with the presence of moderate to severe WMH.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique Identifier: NCT00414583.


Key Words: estimated glomerular filtration rate (eGFR) kidney function MRI stroke white matter hyperintensities (WMH)

Impaired kidney function as well as the presence and severity of white matter disease are associated with an increased risk for subsequent ischemic stroke,1–3 stroke recurrence,4,5 and survival after acute ischemic stroke.6–9 The microvasculature of the human brain and kidney share anatomic as well as functional vasoregulatory similarities.10 Both organs have a low vascular resistance system allowing continuous high-volume perfusion throughout systole and diastole.11,12 In consequence of these evolutionarily emerged vascular similarities of the human brain and kidney, both organs share common vascular risk factors including hypertension and diabetes.13,14 Particularly if untreated, these risk factors predispose to impaired kidney function and white matter brain disease.10,15,16 A strong association between damage in both organs in the young suggests a parallel rather than a subsequent evolution of small-vessel disease in different vascular beds. Such a finding may have preventive implications because it emphasizes the rigorous control of...
small-vessel disease-related risk factors to protect against multiorgan dysfunction already in young and middle-aged persons.

It is established that even a moderately reduced estimated glomerular filtration rate (eGFR) measured by the widely accepted Modification of Diet in Renal Disease formula can be associated with moderate but not clinically relevant kidney impairment. This raises the question if even a mild to moderately decreased eGFR can serve as a predictive marker for the presence and severity of white matter hyperintensities (WMHs) in the human brain already in early disease stages.

The aim of this study was to analyze the association between eGFR with WMH and vascular risk factors in a large cohort of young patients with stroke.

**Methods**

Between April 2007 and January 2010, 5024 young patients with stroke were enrolled in 15 European countries and 47 study centers in the cross-sectional observational Stroke in Young Fabry Patients (SIFAP1) study. The study comprises the largest cohort of young patients with stroke examined so far. Details of this study as well as inclusion and exclusion criteria have been reported previously. In brief, the SIFAP1 study is a multicenter prospective observational study with the primary aim to determine the prevalence of Fabry disease in young (18–55 years) patients with stroke. The secondary aim of the study was to characterize patterns of stroke in young patients collecting a broad range of clinical, laboratory, and radiological data using mandatory stringent standardized methods. Physicians and study nurses interviewed participants and administered a standardized questionnaire to collect data on sociodemographics, clinical symptoms, comorbidities, diagnostics, stroke severity, and etiology. Of the total sample, 4179 individuals had a first-ever stroke. Analysis was restricted to 2903 patients with first-ever ischemic stroke, 233 patients with intracranial hemorrhage, 806 patients with transient ischemic attack, and 237 patients with “other” or unknown types of strokes were excluded (Figure). Of all patients with a first-ever ischemic stroke, complete data sets for eGFR calculation and imaging data for WMH were available in 2009 subjects.

Results of the laboratory blood tests were obtained from medical records. Serum creatinine (mg/dL) was measured either by Jaffe assay or by an enzymatic assay depending on the laboratory study center. According to the study standards, all laboratory facilities of study centers had valid quality management certificates. In addition, all laboratory facilities of German study centers took part in regular “round robin tests” (intercomparison programs) calibrating their facilities to international standards. Kidney function was estimated by the calculated creatinine clearance using the 4-variable Modification of Diet in Renal Disease equation:

\[
\text{eGFR}_{MDRD} = \frac{186 \times \text{Scr}^{-1.154} \times \text{age}^{-0.203} \times 1.210}{\text{if black African or colored African}}
\]

In our analysis, eGFR was used as continuous data. In addition, eGFR was categorized in 3 groups: (1) underfiltration: <60 mL/min; (2) normal filtration: ≥60 to 120 mL/min; and (3) hyperfiltration: ≥120 mL/min. One person with eGFR = 747 mL/min was excluded from further analyses.

Cerebral MRI was mandatory for all study participants. Study centers used standardized MRI sequences and were asked to perform at least T2-weighted and/or fluid-attenuated inversion recovery images and diffusion-weighted imaging sequences. All MR images were analyzed centrally by experienced readers blinded to clinical and demographic data (C.E., F.F., R.Sc.). WMHs were defined as lesions with high signal intensity on T2-weighted images in the absence of evidence for complete tissue destruction and were rated according to the Fazekas scale, which has shown high intra- and interrater reliability. Deep WMHs were classified as 0 = absent;
Risk factors, no. (%)

evidence that punctuate WMH is related to minor often nonischemic
Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria
the first 48 hours or at the time of maximal impairment. The original
of Health Stroke Scale, modified Rankin Scale) was assessed within
once a month (yes versus no). Severity of stroke (National Institutes
consumption was defined as consuming of
5 drinks consumed per day?" Frequency of alcohol consumption
/H11022
rent smoker (yes versus no). Regular drinking was defined as a
standardized questionnaires. Tobacco use was categorized into cur-
lative heart disease, prior myocardial infarction, and/or valvular
disease). Hypertension and dyslipidemia were defined according to
concomitant medication were: diabetes (insulin and/or oral hypogly-
cemics), arterial hypertension, dyslipidemia, and cardiovascular
cemic agents), arterial hypertension, dyslipidemia, and cardiovascu-
lar disease (history of coronary artery, peripheral arterial or congest-
heart disease, prior myocardial infarction, and/or valvular disease). Hypertension and dyslipidemia were defined according to
national guidelines used at each study center. Anthropometric
measurements were obtained at study inclusion. They included
/body mass index (BMI
/H11022
/H11021
lawdwards were: diabetes (insulin and/or oral hypogly-
cents), arterial hypertension, dyslipidemia, and cardiovascular
disease). Hypertension and dyslipidemia were defined according to
national guidelines used at each study center. Anthropometric
measurements were obtained at study inclusion. They included
/body mass index (BMI
/H11022
/year. The original
of Health Stroke Scale, modified Rankin Scale) was assessed within
the first 48 hours or at the time of maximal impairment. The original
Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria
were applied to classify etiology of ischemic strokes.21 Demograph-
ics (age, sex, and ethnicity) were included in the mandatory core data
set collected by centers.

In the first stage, descriptive analyses were conducted. To inves-
tigate linear or quadratic associations among the 3 eGFR groups and
the 3 WMH groups according to sociodemographics and risk factors,
we used logistic, multinomial logistic, ordinal, or linear regression
with random effects to account for the heterogeneity between centers. To ensure numeric stability of the statistical models,
dependent variables were sociodemographics and risk factors. Inde-
pendent variables were eGFR and WMH groups, respectively. In the
second stage, multivariate logistic regression models with random
effects were used to analyze the association of univariate significant
variables (independent variables) with (1) underfiltration versus
normal filtration; (2) hyperfiltration versus normal filtration; and (3)
WMH 0 to 1 versus WMH 2 to 3 as dependent variables. Due to
small numbers in WMH 2 and WMH 3, these 2 groups were
combined into one group. Only variables with significant coeffi-
cients remained in the final model. All statistical analyses were
conducted using IBM SPSS Statistics 19.0.0.1 (SPSS, Inc, IBM
Company, Chicago, IL) and SAS 9.2 (SAS Institute Inc, Cary, NC).
No imputation of missing values was performed; thus, cases with
missing values in at least one variable were not included. A 2-sided
P<0.05 was considered statistically significant. No correction for
multiple testing was carried out.

Results
Demographics and clinical characteristics for the study sam-
ple according to eGFR are shown in Table 1. The mean age
was 45 years (SD=8.3). There were 60.8% men and median National Institutes of Health Stroke Scale (NIHSS) was 4. Of the 2360 patients with first ischemic stroke and available WMH data, 4.4% (n=103) had an eGFR \( \geq \) 60 mL/min, 81.3% (n=1918) an eGFR \( \geq 60 \) to <120 mL/min, and 14.4% (n=339) an eGFR \( \geq 120 \) mL/min. In univariate analyses, eGFR groups were significantly linearly associated with age \( (P<0.001) \), sex \( (P=0.005) \), stroke severity by NIHSS \( (P=0.013) \), hypertension \( (P<0.001) \), cardiovascular disease \( (P=0.005) \), regular alcohol consumption \( (P=0.026) \), higher alcohol consumption \( (P=0.012) \), current smoking \( (P=0.001) \), BMI >25 kg/m\(^2\) \( (P=0.005) \), TOAST criteria \( (P=0.037) \), and WMH \( (P<0.001) \). eGFR groups were significantly quadratically associated with stroke severity by NIHSS \( (P<0.001) \), history of diabetes \( (P<0.001) \), hypertension \( (P<0.001) \), and cardiovascular disease \( (P<0.001) \). There was no group difference regarding hyperlipidemia.

Two multivariate logistic regression models with random effects were used to analyze the association of univariate significant factors with (1) underfiltration versus normal filtration; and (2) hyperfiltration versus normal filtration (Table 2). Compared with normal filtration, underfiltration was independently associated with female sex \( (P<0.001) \), with a history of hypertension \( (P<0.001) \), cardiovascular disease \( (P<0.001) \) and higher WMH grade \( (P<0.010) \), Age, NIHSS, diabetes, regular and higher alcohol consumption, current smoking, BMI >25 kg/m\(^2\), and TOAST were not significant factors in this model. Compared with normal filtration, hyperfiltration was associated with younger age \( (P<0.001) \), male sex \( (P<0.001) \), higher NIHSS score \( (P<0.001) \), a history of diabetes \( (P<0.001) \), current smoking \( (P<0.001) \), fewer BMI >25 kg/m\(^2\) \( (P=0.003) \), and stroke etiology \( (P<0.001) \). History of hypertension, cardiovascular disease, regular and higher alcohol consumption, and WMH grades were not significant (Table 2).

Of the 2500 patients (see the Figure) with first ischemic stroke and available WMH data, 2202 subjects (88.1%) were classified to WMH Grade 0 to 1, 189 subjects (7.5%) to WMH Grade 2, and 109 subjects (4.4%) to WMH Grade 3. The results of univariate analysis of WMH are shown in Table 3. Mean calculated eGFR of subjects was 96.7 mL/min in subjects with WMH 0 to 1, 90.7 mL/min in WMH 2, and 89 mL/min in WMH 3 subjects. Increasing severity of WMH was significantly linearly associated with being older \( (P<0.001) \), having a history of hypertension \( (P<0.001) \), having a BMI >25 kg/m\(^2\) \( (P=0.013) \), and a lower eGFR \( (P=0.009) \). Severity of

### Table 2. Multivariate Logistic Regressions Exploring Factors Associated With Underfiltration and Hyperfiltration

<table>
<thead>
<tr>
<th></th>
<th>Underfiltration (eGFR &lt;60 mL/min)</th>
<th>Hyperfiltration (eGFR ( \geq 120 ) mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>P Value</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age per decade</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Men</td>
<td>0.45</td>
<td>0.28–0.71</td>
</tr>
<tr>
<td>NIHSS†</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.45</td>
<td>2.02–5.88</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2.76</td>
<td>1.52–5.01</td>
</tr>
<tr>
<td>Regular alcohol consumption</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Higher alcohol consumption</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Current smoking</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>BMI &gt;25 kg/m(^2)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td><strong>Stroke etiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large artery atherosclerosis</td>
<td>1.72</td>
<td>1.18–2.52</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>0.95</td>
<td>0.62–1.46</td>
</tr>
<tr>
<td>Small-vessel disease</td>
<td>0.89</td>
<td>0.56–1.42</td>
</tr>
<tr>
<td>Other determined etiology</td>
<td>1.78</td>
<td>1.25–2.55</td>
</tr>
<tr>
<td>Undetermined etiology</td>
<td>Reference</td>
<td>...</td>
</tr>
<tr>
<td>WMH Grade 0–1 Reference</td>
<td>&lt;0.010</td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>2.46</td>
<td>1.34–4.52</td>
</tr>
<tr>
<td>3</td>
<td>1.75</td>
<td>0.75–4.09</td>
</tr>
</tbody>
</table>

Reference in both analyses was the group with normal filtration (under versus normal, n=1666; hyper versus normal n=2167). WMH 0–1= absent or punctuate; WMH 2= early confluent; and WMH 3= confluent.

eGFR indicates estimated glomerular filtration rate; NIHSS, National Institutes of Health Stroke Scale; BMI, body mass index; WMH, white matter hyperintensity.

*Adjusted for center heterogeneity and leaving only variables with significant coefficients in the model.

†Logarithm of NIHSS.
WMH was significantly quadratically associated with cardiovascular disease ($P=0.015$) and current smoking ($P=0.044$). There were no group differences regarding sex, stroke severity, diabetes, hyperlipidemia, regular or higher alcohol consumption.

A multivariate logistic regression model with random effects was used to analyze the association with WMH and univariate significant factors (Table 4). Higher age ($P<0.001$), history of hypertension ($P<0.001$), and lower eGFR ($P=0.010$) were independent risk factors for severity of WMH. Current smoking, cardiovascular disease and BMI $>25 \text{ kg/m}^2$ were not significant in this model.

### Discussion

We analyzed kidney function in the to date largest cohort of young patients with ischemic stroke (≤55 years) of the SIFAP1 study and showed that apart from the well-established risk factors such as age and hypertension, lower eGFR was independently associated with the presence of moderate to severe WMH. As expected, kidney dysfunction (eGFR $<60 \text{ mL/min}$) was associated with hypertension and cardiovascular disease in this cohort. In addition, we showed that kidney hyperfiltration had no association with cerebral WMH but was associated with a distinct risk factor profile compared with underfiltration. The frequencies of genetically determined vascular diseases such as Fabry disease or cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy with WMH 2 to 3 were very low in our cohort and thus had no impact on our observations.

Associations between clinically significant impaired kidney function and WMH have been demonstrated in elderly patients with stroke.\cite{13,22} Furthermore, in young patients with ischemic stroke, leukaraiosis and silent brain infarction were shown to be more frequent in those with kidney dysfunction.\cite{7} Our findings now indicate a relationship between even moderately decreased kidney function and WMH reflecting small-vessel disease. However, kidney dysfunction was not preferentially associated with small-vessel disease classified according to the TOAST classification in our analysis.

Table 4. Multivariate Logistic Regression Associated With Higher Grades of WMH (2–3 versus 0–1; $n=1996^*$)

<table>
<thead>
<tr>
<th>Risk factors, no. (%)</th>
<th>OR</th>
<th>95% CI</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in 10 y</td>
<td>2.19</td>
<td>1.70–2.81</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Current smoking</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.98</td>
<td>1.46–2.69</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>BMI $&gt;25 \text{ kg/m}^2$</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>eGFR, mL/min, mean (SD)</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
</tr>
</tbody>
</table>

WMH indicates white matter hyperintensity; BMI, body mass index; eGFR, estimated glomerular filtration rate; OR, odds ratio; CI, confidence interval.

*Adjusted for center heterogeneity and leaving only variables with significant coefficients in the model.
Type 2 but not with Type 1 diabetes. Diagnosis of diabetes was more frequent in the hyperfiltration group compared with the normal filtration group in our cohort, but we could not differentiate between Types 1 and 2 diabetes. Interestingly, patients of the high eGFR group showed least brain WMH.

Current smoking and a low BMI were also significantly more frequent in the hyperfiltration group. As proposed before, such associations to diabetes or smoking might reflect early damage of the renal vascular bed. The association of large-artery disease in the TOAST classification to hyperfiltration has to be interpreted with caution.

In contrast to other findings, higher alcohol consumption was not associated with the high eGFR group but tended to be more frequent in this hyperfiltration group than previously reported. The association between low BMI with hyperfiltration is probably due to the younger age and male sex in this group but needs further investigations. In other cross-sectional studies obesity was associated with hyperfiltration, suggested to predispose early kidney damage and chronic kidney disease.

The association of WMH in patients with impaired kidney function could be explained as a consequence of exposure to the same vascular risk factors and as an expression of the same common vascular risk. As a consequence of anatomic and vasoregulatory similarities, the vascular risk factors age, hypertension, and diabetes damage both renal and cerebral vascular bed in parallel, which is represented as decreased kidney function and increased WMH in the human brain. Involved vascular mediators of damage cascades are controversial. Nevertheless, nitric oxide generated by endothelial nitric oxide synthase plays a crucial role in vascular function and homeostasis. Nitric oxide deficiency, which can occur in renal disease, could therefore act as a potential target in preventive strategies.

Renal dysfunction in acute stroke is an independent predictor for long-term mortality and cerebral WMHs in stroke are associated with bad outcome and recurrent strokes. One might speculate that early surrogate markers of kidney function impairment such as eGFR or microalbuminuria might also serve as early indicators of vascular brain damage as well. In this context, measurement of eGFR should be discussed as a surrogate parameter for stroke risk stratification indicating those patients who could benefit from intensified secondary prevention therapy strategies. However, regardless of the parallelism between the development of WMH and impairment of renal function, there still may be other separate or mutual yet unexplored pathophysiological mechanisms.

Limitations
Our study is limited by its cross-sectional study design, which does not allow assessing the impact of our findings on the individual patient’s outcome after first ischemic stroke. In addition, the time point of blood sampling was not specifically standardized although occurred always in the acute phase and kidney function was calculated using serum creatinine-based formulas only. Additional measurement such as collection of 24-hour urine or urinary albumin measurement in combination with estimated eGFR would allow a more precise assessment of kidney function. However, the Modification of Diet in Renal Disease formula is widely accepted as a valid surrogate of kidney function. A further limitation is that we were not able to analyze the interactions of different characteristics of hypertension (eg, duration, type, severity) and diabetes (differentiation between Types 1 and 2) in more detail. We cannot rule out a selection bias in our cohort because patients with available data on eGFR (n = 2360) had more often hypertension, and patients with available data on WMH (n = 2500) had a lower NIHSS score as compared with those not included, respectively. Like in our study, the TOAST classification was done in the local study centers; TOAST classification might have been influenced by the information on vascular risk factors or by imaging findings. However, crosschecks of TOAST and imaging findings revealed only a small percentage of misclassified patients. Finally, the relatively small number of patients with moderate (8%) and severe WMH (4%) might have limited the scope of this analysis; extrapolating our results to the typically elder common stroke population is still limited by the young mean age of our study cohort and interpretation of the results could be limited because powerful risk factors were only controlled statistically.

In conclusion, our study revealed in the largest study on young patients with stroke that besides the known risk factors age and hypertension, even a moderately reduced kidney function, as measured by decreased eGFR, was associated with the severity and burden of WMH.

Acknowledgments
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Disclosures
None.

References


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