Microalbuminuria in Ischemic Stroke

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Objectives: To determine (1) the incidence of microalbuminuria in patients with recent ischemic stroke, (2) its relationship to risk factors for stroke, (3) its prevalence in the major subtypes of ischemic stroke, and (4) its potential for identifying patients at increased risk for recurrent stroke, myocardial infarction, or vascular death.

Design: Prospective case-control study.

Setting: Outpatient clinics at the medical centers affiliated with the Department of Veterans Affairs and Oregon Health Sciences University in Portland, Ore.

Patients: A total of 186 older men and women (median age, 65 years) who were enrolled in a prospective study of risk factors for recurrent stroke, including 97 patients with recent (6-8 weeks) ischemic stroke, 51 with similar clinical risk factors for stroke, including 24 with a history of remote stroke or transient ischemic attack, and 38 community-dwelling volunteers.

Results: Microalbuminuria was 3 times more prevalent in patients with recent stroke (29%) than in those with clinical risk factors for stroke (10%), and was undetectable in healthy elderly controls (P<.001). The presence of microalbuminuria in recent stroke as well as in the combined recent and remote stroke or transient ischemic attack group (n = 121) was predicted by diabetes (odds ratio [OR], 8.4; 95% confidence interval [CI], 2.6-27.0; P<.001; serum albumin levels (OR, 0.12; 95% CI, 0.03-0.50; P<.005); age (OR, 1.1; 95% CI, 1.0-1.2; P=.01), and ischemic heart disease (OR, 3.0; 95% CI, 1.0-9.1; P=.05). Among patients with recent stroke the prevalence of microalbuminuria did not differ among major ischemic stroke subtypes, ie, atherothrombotic, 23%; cardioembolic, 30%; and lacunar, 33%. During a mean ± SD of 1.5 ± 0.9 years of follow-up, 20% of patients with recent stroke, 14% with risk factors for stroke, and 0% of healthy elderly volunteers had vascular end points (P<0.004), with events being as frequent in patients with microalbuminuria (32%) as in patients with macroalbuminuria (33%). After controlling for major clinical risk factors, microalbuminuria remained an independently significant predictor of future stroke in the combined recent stroke and remote stroke or transient ischemic attack group (Cox proportional hazard ratio, 4.9; 95% CI, 1.4-17.6; P<.01).

Conclusions: Microalbuminuria is a common finding in patients with cerebrovascular disease and is associated with increased risk for stroke even after correction for the presence of confounding clinical risk factors. These data suggest that microalbuminuria merits further examination as a potentially inexpensive and easily measured marker of increased risk for stroke.

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Although microalbuminuria is associated with clinical risk factors for stroke, including diabetes, hypertension, aging, history of myocardial infarction, and left ventricular hypertrophy, there is surprisingly little information regarding it as an independent risk factor for stroke or as a predictor of stroke outcome. A large prospective study has reported that microalbuminuria is a risk factor for stroke in men, and a limited case-control study found that the highest quintile of microalbuminuria values was associated with a 13-fold increased risk for stroke. Although microalbuminuria is more prevalent in diabetes and/or hypertension, 2 classic risk factors associated with intracranial arteriosclerosis, reduced microvascular perfusion, and lacunar infarcts, there is scant data regarding the incidence of microalbuminuria in lacunar stroke. More recently, a highly significant association between microalbuminuria and carotid artery intima-media thickness has been reported, a finding which suggests that microalbuminuria may be a marker for early development of carotid artery atherosclerosis and points to a possible linkage between microalbuminuria and atherothrombotic stroke mechanism. With the introduction of more sensitive and relatively inexpensive dipstick methods, patients can now be readily screened for microalbuminuria, commonly defined as a urinary albumin concentration higher than 20 but not exceeding 200 mg/L. Our study was designed, therefore, to determine (1) the incidence of microalbuminuria in ischemic stroke, (2) its relationship to risk factors for stroke, (3) its prevalence in major subtypes of ischemic stroke, and (4) its potential use as a marker for stroke recurrence.

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PATIENTS AND METHODS

Patients with recent ischemic stroke (≤7 days), patients with multiple clinical risk factors for stroke such as hypertension, diabetes, and ischemic heart disease (IHD), and healthy elderly controls were recruited from the wards and clinics of the Portland Veterans Administration and Oregon Health Sciences University hospitals in Portland after giving informed consent according to institutional guidelines. Patients with a history of stroke and/or transient ischemic attack were eligible for the risk group provided they had experienced no cerebrovascular symptoms for at least 6 months prior to enrollment. Patients with urinary tract infection, chronic renal failure, malignancy, and vasculitis were excluded. A detailed description of additional exclusions, diagnostic criteria for risk factor assessment, and definition of vascular end points has been published.2 Vascular end points included recurrent stroke, myocardial infarction, and vascular death; transient ischemic attacks were noted but not counted as end points. Participants in all groups were examined at enrollment, 6 to 8 weeks, 6 months, 1 year, and once a year thereafter until termination of the study or the occurrence of a vascular event.

To minimize potentially confounding factors present at onset of stroke, urinary albumin levels in the recent stroke group were studied at the first outpatient clinic visit 6 to 8 weeks after the indexing infarction. Collection kits and instructions for obtaining first morning void urine samples on 2 consecutive days were mailed to patients prior to clinic. Urine samples were kept at 4°C for a maximum of 3 days for batch analysis by rate nephelometry at the Oregon Health Sciences University clinical laboratory (Beckman-Coulter Instruments, Fullerton, Calif). Duplicate determinations were performed on samples from each day and the results averaged. Normoalbuminuria was defined as a urinary albumin concentration 20 mg/L or lower, microalbuminuria as higher than 20 mg/L but lower than 200 mg/L, and macroalbuminuria as higher than 200 mg/L. Statistical analysis, including analysis of variance with Bonferroni post hoc correction or Kruskal-Wallis for evaluating intergroup differences, χ² or Fisher exact test for assessing differences in frequency distributions, as well as Kaplan-Meier survival curves, was performed with Stata software (Stata 5.0; Stata Corporation, College Station, Tex). Except when stated otherwise, summary statistics are expressed as the mean ± SD.

RESULTS

As shown in Table 1, the recent stroke (n = 97) and risk (n = 51) groups had similar percentages of patients with hypertension, diabetes, IHD, and other classic risk factors for stroke, except for more current smokers in the recent stroke group (P < .003). More than half (54 [56%]) of the patients with recent stroke had experienced a lacunar infarction, followed by 22 (23%) with atheroembolic and 20 (21%) with cardioembolic mechanisms. Since nearly half (24 [47%]) of the patients in the risk group had a history of remote stroke or transient ischemic attack, they were combined with patients with recent stroke into a cerebrovascular disease (CVD) group (n = 121) for additional analysis. The clinical characteristics of the combined CVD group (Table 1) did not differ significantly from those of the parent groups. The 38 healthy controls were age balanced (average age, 60 ± 8 years) with the patients with recent stroke and risk factors, and the racial composition of all groups was predominantly white (97%).

Microalbuminuria was more prevalent in the stroke (29%) compared with the risk (10%) or healthy elderly groups (0%) (P < .001). An additional 10% of patients with recent stroke and 10% of patients with risk factors had macroalbuminuria. In the combined CVD group, 26% were microalbuminuric and 8% were macroalbuminuric. Diabetics and IHD, but not hypertension (Table 2) were twice as common in both the microalbuminuric and macroalbuminuric groups as in the normoalbuminuric group. Approximately 40% of patients with microalbuminuria and macroalbuminuria were insulin-dependent diabetics, but with the exception of insulin (P < .006), no relationship was observed between patterns of medication use and urinary albumin levels. Fasting blood glucose was elevated in both albuminuric subgroups, but glycated hemoglobin, although elevated, did not differ significantly by albumin status (glycosylated hemoglobin available for 69% of patients with normoalbuminuria, 58% with microalbuminuria, and 80% with macroalbuminuria). Neither glucose nor glycated hemoglobin levels correlated with absolute levels or urinary albumin (data not shown), nor did serum creatinine levels differ significantly among albumin subgroups. Finally, the prevalence of microalbuminuria did not differ among the 3 major subtypes of ischemic stroke, ie, atheroembolic mechanisms, 23%; cardioembolic mechanism, 30%; or lacunar infarction, 32%, even though patients with lacunar infarction had a higher incidence of diabetes, hypertension, or both (90%), than patients with cardioembolic (63%) or atheroembolic (72%) stroke mechanism (P < .03).

Both in the recent stroke and the combined CVD groups the presence of the same 4 risk factors indepen-

Table 1. Population Description

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recent Stroke (n = 97)</th>
<th>Risk (n = 51)</th>
<th>Combined† (n = 121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microalbuminuria</td>
<td>29</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>Mean ± SD age, y</td>
<td>66 ± 8</td>
<td>67 ± 9</td>
<td>66 ± 8</td>
</tr>
<tr>
<td>Male</td>
<td>93</td>
<td>76</td>
<td>89</td>
</tr>
<tr>
<td>Diabetes</td>
<td>38</td>
<td>31</td>
<td>39</td>
</tr>
<tr>
<td>Hypertension</td>
<td>79</td>
<td>75</td>
<td>79</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>53</td>
<td>55</td>
<td>53</td>
</tr>
<tr>
<td>LV hypertrophy‡</td>
<td>14</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Current smoker</td>
<td>34</td>
<td>129</td>
<td>30</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>29</td>
<td>37</td>
<td>39</td>
</tr>
</tbody>
</table>

*Values are percentages unless otherwise indicated.
† Patients with recent stroke and risk factors for stroke with a history of remote stroke or transient ischemic attack.
‡ Left ventricular (LV) hypertrophy by electrocardiographic criteria.
§ P < .003, Fisher exact test.
dently predicted microalbuminuria: diabetes, serum albumin, age, and IHD. For the combined group the odd ratios for diabetes was 8.4 (95% confidence interval [CI], 2.6-27.0; \( P < .001 \)); for albumin, 0.12 (95% CI, 0.03-0.50; \( P < .005 \)); age, 1.1 (95% CI, 1.0-1.2; \( P < .01 \)); and for IHD, 3.0 (95% CI, 1.0-9.1; \( P < .05 \)). Although it was not an independent predictor, the degree of carotid stenosis detectable by ultrasonography performed on 76% of the combined CVD group was positively related (\( P < .04 \)) to urinary albumin levels, ie, in patients with normoalbuminuria, microalbuminuria, or macroalbuminuria.

During 1.5 ± 0.9 years of follow-up, 20% of the patients with recent stroke, 14% with risk factors for stroke, and 0% of the healthy elderly controls had new vascular end points (\( P < .004 \)). As shown in Figure 1, vascular events were common among patients with recent stroke who had microalbuminuria (32%) and macroalbuminuria (33%), with both groups having 3 times more events than patients with normoalbuminuria (12%) (\( P < .04 \)). After controlling for the presence of diabetes, hypertension, and smoking status, microalbuminuria was not an independent predictor of recurrent stroke (\( P < .06 \) in those with recent stroke. In the combined CVD group, however, microalbuminuria remained a significant marker for future stroke, after correction for the same 3 risk factors: hazard ratio (Cox proportional model), 4.9 (95% CI, 1.4-17.6; \( P < .01 \)). The Kaplan-Meier plot (Figure 2) illustrates the reduced survival probability for patients with CVD plus microalbuminuria compared with their counterparts with normoalbuminuria (\( P < .03 \), Mantel-Haenszel). Notably, macroalbuminuria was not predictive for stroke in either group, since all vascular events in patients with macroalbuminuria consisted of myocardial infarction or death.

**COMMENT**

Although rare (0%-4%) in clinically healthy population-based samples, microalbuminuria may be present in up to one fourth of patients with cardiovascular risk factors, most notably those with diabetes, hypertension, coronary artery disease, and/or smoking habit.8,11 Consistent with this literature, microalbuminuria was not found in healthy elderly subjects but was present in 10% of those

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Table 2. Urinary Albumin Status in Combined CVD Group*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Normoalbuminuric (n = 80)</th>
<th>Microalbuminuric (n = 31)</th>
<th>Macroalbuminuric (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD age, y</td>
<td>65 ± 8</td>
<td>69 ± 7</td>
<td>66 ± 7</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>26 (.001)†</td>
<td>61</td>
<td>70</td>
</tr>
<tr>
<td>Insulin dependent, %</td>
<td>14 (.006)†</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>Ischemic heart disease, %</td>
<td>44 (.02)†</td>
<td>71</td>
<td>70</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>75</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>26</td>
<td>32</td>
<td>50</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary albumin, mg/L</td>
<td>7 ± 5</td>
<td>71 ± 47 (NS)</td>
<td>875 ± 954 (( P &lt; .001 ))†</td>
</tr>
<tr>
<td>Serum albumin, g/L</td>
<td>4.1 ± 0.4</td>
<td>3.9 ± 0.4 (( P &lt; .04 ))</td>
<td>3.6 ± 0.7 (( P &lt; .001 ))†</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.2 ± 0.3</td>
<td>1.5 ± 0.9 (NS)</td>
<td>1.5 ± 0.7 (NS)‡</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>108 ± 36</td>
<td>161 ± 72 (( P &lt; .004 ))</td>
<td>180 ± 105 (( P &lt; .02 ))†</td>
</tr>
<tr>
<td>Glycosylated hemoglobin, %</td>
<td>7.7 ± 2.5</td>
<td>8.4 ± 2.4 (NS)</td>
<td>9.8 ± 2.7 (NS)‡</td>
</tr>
</tbody>
</table>

*Combined cerebrovascular disease (CVD) indicates patients with stroke and risk factors with history of stroke or transient ischemic attack; normoalbuminuric, urinary albumin level lower than 20 mg/L; microalbuminuric, higher than 20 but lower than 200 mg/L; macroalbuminuric, higher than 200 mg/L, and NS, not significant. †Significant of difference, Fisher exact test. ‡\( P \) value for difference for normoalbuminuric, corrected analysis of variance.

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Figure 1. Compared with patients with normoalbuminuria, both patients with microalbuminuria and macroalbuminuria with recent stroke had significantly more new vascular events (stroke, myocardial infarction, or vascular death) during the mean ± SD of 1.5 ± 0.9 years of follow-up.

Figure 2. Patients with cerebrovascular disease (either recent stroke or remote stroke or transient ischemic attack) with microalbuminuria had significantly lower probability of surviving free of a recurrent vascular event (those with macroalbuminuria excluded).
with risk factors for stroke. However, the high prevalence (29%) of microalbuminuria in patients with recent stroke compared with those with a similar risk profile (10%) is a new and unexpected finding. Although microalbuminuria is thought to be a marker for vascular endothelial damage due to the severity and/or duration of numerous pathophysiological insults, especially the injurious effects of poorly controlled diabetes and hypertension, this view fails to account for increased microalbuminuria in recent stroke. Specifically, the patients with recent stroke and those with risk factors for stroke did not differ with respect to the percentages of patients with hypertension or diabetes (Table 1), the proportion of insulin-dependent patients with diabetes (56% in each group), glycemic control (8.2 ± 2.7 vs 7.3 ± 2.0% glycosylated hemoglobin), or the duration of hypertension (11 ± 12 vs 12 ± 10 years). Although creatinine clearance was not assessed, serum creatinine levels did not differ significantly between the groups with recent stroke (1.3 ± 0.6 mg/dL) and risk factors for stroke (1.1 ± 0.2 mg/dL). As noted earlier, the group with recent stroke included more current smokers (34% vs 12%; \( P < .003 \)) than the group with risk factors; although smoking status was not an independent predictor of urinary albumin levels in this study, current smoking may have contributed to the higher prevalence of microalbuminuria in recent stroke.

Diabetes was clearly the clinical factor most closely related to microalbuminuria in both patients with recent stroke and the combined group with CVD; however, age and IHD were also significant, as has been reported. Yet even though microalbuminuria was significantly related to IHD, we could not confirm the relationship between microalbuminuria and left ventricular hypertrophy observed by others. Serum albumin levels were also an independent (negative) predictor of microalbuminuria in the population with stroke, a finding which agrees with some studies showing increased transcapillary escape of albumin in patients with albuminuria. Moreover, the association between microalbuminuria and carotid stenosis in this article provides additional indirect support for the reported correlation between microalbuminuria and increased carotid artery intima-media thickness or carotid wall thickness in both patients with and without diabetes.

Although direct comparison with earlier studies is difficult due to methodological differences, our data are in overall agreement with findings on 38 patients with mixed ischemic and hemorrhagic stroke, as well as with results of a large (n = 2302) prospective study of first-ever stroke in Japan, which found that urinary albumin (dipstick method for macroalbuminuria) represented an increased risk for stroke (relative risk, 3.33; odds ratio, 1.38-8.02) in men but not women. Although we had speculated that microalbuminuria might be a marker for lacunar infarcts, given this group’s higher combined incidence of diabetes and/or hypertension, the results of our study confirm an earlier report of no significant difference in the prevalence of microalbuminuria among different subtypes of stroke.

This study is, to our knowledge, the first to examine the relationship between urinary albumin levels and recurrent vascular events in patients with CVD. Patients with recent stroke and microalbuminuria were more likely to experience a recurrent stroke; yet, as noted earlier, after adjusting for diabetes, smoking, and hypertension, microalbuminuria was only weakly prognostic (\( P < .06 \)). However, in patients with a history of recent or remote stroke or transient ischemic attack, microalbuminuria was an independent marker for future stroke (\( P < .01 \)), even after correction for the above risk factors. Thus, although identification of markers for individuals at increased risk for stroke has been problematic, these data support the view that microalbuminuria merits further scrutiny as a potentially inexpensive and easily measured marker for heightened risk of stroke in patients who have CVD.

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REFERENCES


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