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Metabolic Syndrome and Its Components as Predictors of Ischemic Stroke in Type 2 Diabetic Patients

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Background and Purpose—The available data regarding the association between metabolic syndrome (MS) or MS components and ischemic stroke in type 2 diabetics are limited and inconsistent. This study aimed to investigate these associations.

Methods—Five hundred ninety-nine consecutive type 2 diabetic patients (mean age 60.4±9.6 years, 54% men) were followed-up for 10.1 years (median period). Baseline clinical and laboratory characteristics and the occurrence of a first-ever ischemic stroke during follow-up were recorded.

Results—Seventy-eight patients developed a first-ever ischemic stroke. According to Cox proportional hazard model, waist circumference (hazard ratio, HR:1.006, 95% CI:1.002 to 1.010, $P=0.003$) and age (HR:1.061, 95% CI:1.002 to 1.125, $P=0.04$) were significant predictors. After incorporating various combinations of MS components in multivariate models, only age and waist circumference remained significant.

Conclusions—MS per se at baseline or combinations of its components do not predict the development of ischemic stroke in type 2 diabetic patients. Waist circumference represents an independent prognostic factor and could be used as a clinical tool for stroke prevention in this population. **(*Stroke*. 2008;39:1036-1038.)**

Key Words: ischemic stroke ■ metabolic syndrome ■ risk factors ■ type 2 diabetes

Dyslipidemia, obesity, and hypertension are common comorbidities that contribute to the increased stroke risk in patients with type 2 diabetes.[1] These risk factors, along with abdominal obesity, represent components of the metabolic syndrome (MS).[2] Of note, the evidence regarding the association between MS, its components, and stroke risk is limited and inconsistent, especially in the diabetic population.[3,4] In this study, we examined whether the individual components of MS or their specific combinations have a different predictive value for ischemic stroke in type 2 diabetic patients than the presence of MS alone.

Subjects and Methods

A total of 599 consecutive type 2 diabetics without known cardiovascular disease were prospectively recruited over a period of 5 years and were followed-up for a median period of 10.1 years (8.2 to 13.4 years). The following parameters were determined at baseline: presence of MS, number of MS components, age, sex, blood pressure, total cholesterol, LDL-cholesterol, triglycerides, HDL-cholesterol, glycosylated hemoglobin (HbA_{1C}), smoking status, and diabetes duration. MS was diagnosed according to the National Cholesterol Education Program/Adult Treatment Panel III criteria.[2] Individuals receiving antihypertensive medications were considered hypertensive regardless of blood pressure measurements. Each patient was tested for proteinuria and retinopathy.

All participants gave written informed consent and the Institutional Ethics Committee approved the study protocol.

Stroke incidents were obtained from departmental outpatient database, local hospitals' discharge diagnoses, and self-reported disease history. The diagnosis of a first-ever ischemic nonembolic stroke in each case was validated by a consultant neurologist. The study protocol included a brain CT scan at the acute phase to detect intracerebral or subarachnoid hemorrhage, a carotid Doppler ultrasound to exclude a potential embolic cause and a new brain CT scan to confirm ischemic stroke, as indicated. Electrocardiographic and transthoracic echocardiographic studies were performed to exclude potential embolic sources. Subjects with a history of stroke, atrial fibrillation, valvular heart disease, endocarditis, pulmonary vein thrombosis, atrial myxoma, stable angina, recent acute coronary syndrome, peripheral artery disease, infections, or diagnosed as having transient ischemic attack were excluded.

Statistical Analysis

Baseline characteristics were analyzed using Student t test and χ^2 test as appropriate. Survival analysis methodology was used to evaluate the time until the occurrence of stroke (end point). To determine the impact of MS, its constituents and the cumulative number of MS components on stroke risk, a multivariate Cox proportional hazards regression was used that included as explanatory variables: MS

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Table 1. Baseline Characteristics of the Study Population

	Nonstroke (n=521)	Incident Cases (n=78)	*P* Value
Age, years	59.7±9.7	64.8±7.2	<0.001
Men, %	46.5	41.5	NS
Body mass index, kg/m^2	28.4±4.7	29.2±5.2	NS
Current smokers, %	36.4	30.5	NS
Systolic blood pressure, mm Hg	140.8±122.4	148.3±23.3	0.006
Diastolic blood pressure, mm Hg	82.3±8.5	84.1±10.4	NS
Waist, cm	100.9±14.9	101.5±10.8	NS
Triglycerides, mg/dL	174.1±125.5	176.9±85.6	NS
HDL-cholesterol, mg/dL	46.0±22.4	48.7±12.4	NS
LDL-cholesterol, mg/dL	154.87±45.74	171.56±53.54	0.038
Total cholesterol, mg/dL	238.17±48.02	252.97±62.43	0.043
Diabetes duration, years	9.8±8.5	11.9±8.3	0.036
HbA_{1C}, %	7.2±1.6	7.4±1.7	NS
Metabolic syndrome, MS, %	61.8	66.7	NS
Prevalence of MS components			
Waist [>102 cm (men); 88 cm (women)], %	16	29	0.015
Hypertension, %	54.6	67.9	0.021
HDL-cholesterol [<40 (men or <50 mg/dL (women)], %	52	47	NS
Triglycerides ≥150 mg/dL, %	50.3	56.1	NS

NS indicates not significant.

(categorical variable), its constituents (continuous variables), and the number of MS criteria (ordinal variable receiving values from 1 to 5). Additional models were run that incorporated various potential stroke risk factors as covariates: gender, age, smoking, body mass index, HbA_{1C}, lipids, and diabetes duration. Significance levels were set at $P<0.05$. All statistical analyses were performed with SPSS 13.0 (SPSS Inc).

Results

Baseline characteristics of the study population and the corresponding prevalence of MS components are presented in Table 1. Seventy-eight subjects developed an ischemic stroke during follow-up. In univariate analysis, stroke incident correlated with systolic blood pressure, waist circumference, and low HDL-cholesterol levels, but not with MS as an entity (Table 2). After performing a multivariate Cox model (stepwise-analysis), only waist circumference was significantly associated with stroke risk (Table 2).

In a multivariate Cox regression model incorporating various stroke risk factors, with the exception of both MS and its constituents, age was the single factor to correlate with stroke (Table 3).

With regard to the effect of MS component combinations on stroke risk, subjects fulfilling the triad consisting of diabetes, hypertension and high triglyceride levels had a 63% (hazard ratio, HR=1.63, 95% CI: 1.178 to 2.849, $P=0.007$) higher risk of developing stroke. Nevertheless, when age, waist circumference and the combination of diabetes-hypertension-elevated triglycerides were modeled together, only age (HR=1.058, 95% CI: 1.001 to 1.124, $P=0.028$) and waist circumference (HR=1.029, 95% CI: 1.012 to 1.068,

Table 2. Results of Cox Hazards Regression Analysis Associating MS and Its Components With Stroke as End Point

Covariates	HR	95% CI	*P* Value
Univariate analysis			
MS	1.166	0.801–2.044	0.113
Waist circumference, cm	1.011	1.009–1.049	0.002
Systolic blood pressure, mm Hg	1.015	1.005–1.024	0.033
Triglycerides, mg/dL	1.032	0.900–1.153	0.137
HDL-cholesterol, mg/dL	0.978	1.003–1.039	0.031
No. of MS components	1.020	0.822–1.265	0.858
Multivariate stepwise-analysis			
Waist circumference, cm	1.009	1.005–1.048	0.002

Table 3. Results of Multivariate Cox Regression Analysis for Potential Prognostic Factors of Stroke in Type 2 Diabetics

Covariates	HR	95% CI	*P* Value
Sex	1.210	0.574–1.381	0.204
Age, years	1.061	1.003–1.132	0.022
Smoking	1.152	0.532–1.263	0.203
Body mass index, kg/m^2	0.976	0.792–1.083	0.406
HbA_{1C}, %	1.001	0.681–1.007	0.281
Total cholesterol, mg/dL	1.005	0.796–1.019	0.119
Diabetes duration, years	1.008	0.984–1.134	0.106
LDL-cholesterol, mg/dL	1.009	0.992–1.014	0.073
Retinopathy	1.297	0.816–1.610	0.302
Proteinuria	1.048	0.720–1.786	0.344

$P=0.004$) remained significant predictors. After controlling for age, a 10-cm increase in waist circumference was associated with a 5.8% higher risk of ischemic stroke. Incorporation of available data regarding new onset of medications, including statins, and antiplatelet agents, in the previous models did not influence the results of the analyses.

Discussion

The present study demonstrates that waist circumference and age represent significant predictors of first-ever ischemic stroke in type 2 diabetics independent of body mass index and other traditional risk factors. No association was found between stroke and the presence of MS per se at baseline, or the cumulative number of MS components. The relatively low prevalence of MS and hypertension observed in our diabetic population compared to other studies[5] could be attributed to the relatively low mean age and the adoption of a Mediterranean diet[6] by Greek patients.

Our results are consistent with earlier large-scale epidemiological studies, which showed no association between stroke and conventional cardiovascular risk factors, including dyslipidemia, in diabetic patients,[7] thus supporting the notion that the atherosclerotic process in the intracranial vascular bed may be different than that occurring in coronary arteries.

In accordance with earlier reports, waist circumference, as a measure of abdominal obesity, was a strong predictor of ischemic stroke.[8] The effect of abdominal adiposity on stroke risk is possibly mediated, in part, by the intense endocrine activity of intra-abdominal adipocytes via secretion of adipokines (leptin, TNF-α, interleukin-6, resistin, and adiponectin), and indirectly through insulin resistance.[3,9] Other relevant mechanisms include dyslipidemia, hypertension, prothrombotic and proinflammatory states, which commonly coexist in obese subjects and strongly predict the cardiovascular outcomes.[9–11]

In summary, waist circumference could be a useful clinical tool in identifying type 2 diabetic patients at high-risk of ischemic stroke independent of other established cardiovascular risk factors. Whether intra-abdominal adiposity should be included in strategies aiming at preventing stroke incidents in type 2 diabetes needs to be further tested.

Disclosures

None.

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