Diabetes and Stroke

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ABSTRACT

Diabetes mellitus is a well-established independent risk factor for stroke and is associated with high mortality. Risk factors or risk markers for a first stroke were classified according to their potential for modification (nonmodifiable, modifiable, or potentially modifiable) and strength of evidence (well documented or less well documented). Modifiable risk factors include hypertension, exposure to cigarette smoke, diabetes, atrial fibrillation and certain other cardiac conditions, dyslipidemia, carotid artery stenosis, sickle cell disease, postmenopausal hormone therapy, poor diet, physical inactivity, and obesity and body fat distribution. Some of parameters are useful as screening test to predict the incidence of stroke in diabetic patients in the future, such as UKPDS Risk Engine, incidence of carotid bruit featuring the stenosis of carotid artery, QTc interval prolongation and proteinuria. The real action must be taken to prevent the stroke when high risk patient is found. The modifiable and potentially modifiable risk factors that have been recommended by numbers of expert committee have to be modified immediately. In case with stenosis of carotid artery, the endarterectomy and carotid stenting have become popular and acceptable treatment in USA and Europe. It must be considered by Indonesian physicians to decrease the incidence of stroke.

Key words: diabetes mellitus, stroke, coronary heart disease.

INTRODUCTION

Coronary heart disease is the most confronting disease in many countries. It’s death rate always becomes first rank. The World Health Organization (WHO) estimates countries such as China, India, and Russia could lose $200 billion to $550 billion in their gross domestic product in the next 10 years because of heart disease, stroke, and diabetes.1

Diabetes mellitus is a well-established independent risk factor for stroke and is associated with high mortality. This increased risk has been linked to the pathophysiological changes seen in the cerebral vessels of patients with diabetes.2 Major risk factors for stroke include increase of blood pressure, diabetes mellitus, smoking and high serum LDL cholesterol. In patients with several background of condition or disease, such as coronary heart disease, left ventricular hypertrophy, atrial fibrillation and peripheral vascular disease, the incidence of stroke increases significantly.3 The increase risk of stroke seen in hyperglycemic subjects and those with elevated serum insulin levels at screening reflected to some extent the high proportion of men who have subsequently developed diabetes.4 Two of 3 diabetic patients died by coronary heart disease and stroke. The association of diabetes, heart disease and stroke remains to be further studied.

Recent studies showed that 60% of diabetic patient suffering from high blood pressure and abnormality of lipid profile such as high serum triglyceride, low serum HDL cholesterol, and high serum LDL cholesterol were detected in almost all of them. The strong association of diabetes with risk of stroke, especially strokes that are due to vascular disease and infarction is well established. The relationship between transient cerebral ischemia and stroke was less consistent than completed stroke. Studies have also shown a strong relationship between subclinical vascular disease, both in the carotid and lower extremities and diabetes, and higher risk of stroke.5 The association between stroke and diabetes is varied widely according to race/ethnic, sex and the age of patients. Stroke death rate are higher in African Americans than

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whites, but the age-adjusted stroke death rates for Asian-Pacific Islanders, Native Americans, and Hispanics are lower than whites. Stroke rate in diabetic women is higher than in diabetic men. Diabetes is clearly one of the most important risk factors for ischemic stroke, especially in patients less than 65 years of age with the age of 45-55 years of age which are the peak of rate of stroke in diabetic patients. The majority of acute stroke patients have disorders of glucose metabolism, and in most cases this fact has been unrecognized. Diabetes worsens the outcome of acute stroke. Therefore, in the post–acute phase, an oral glucose tolerance test should be recommended in all stroke patients with no prior history of diabetes.

**RISK FOR STROKE IN DIABETIC PATIENT**

Risk factors or risk markers for a first stroke were classified according to their potential for modification (nonmodifiable, modifiable, or potentially modifiable) and strength of evidence (well documented or less well documented). Nonmodifiable risk factors consist of age, sex, low birth weight, race/ethnicity, and genetic factors. Well-documented and modifiable risk factors consist of hypertension, exposure to cigarette smoke, diabetes, atrial fibrillation and certain other cardiac conditions, dyslipidemia, carotid artery stenosis, sickle cell disease, postmenopausal hormone therapy, poor diet, physical inactivity, and obesity and body fat distribution. Less well-documented or potentially modifiable risk factors include the metabolic syndrome, alcohol abuse, drug abuse, oral contraceptive use, sleep-disordered breathing, migraine headache, hyperhomocysteinemia, elevated lipoprotein (a), elevated lipoprotein-associated phospholipase, hypercoagulability, inflammation, and infection.

Diabetes is clearly one of the most important risk factors for ischemic stroke. Commonly the relative risk of stroke in diabetic patient is higher than nondiabetic, but the rate of relative risk is width and varies by different studies. (Table 1, Table 2, Figure 1) In black diabetic American, the peak rate of risk for stroke (8-10 times higher) is at the age of 34-45 years, but in the same area, the whites have 2.6-5.3 of relative risk for stroke. The highest risk for stroke for white diabetic American is at the age of 45-64 years. About 37-42% of all incidences of stroke are associated with diabetes alone or combination diabetes and hypertension.5 One-third of all acute stroke patients may have diabetes mellitus. For patients presenting with post-stroke hyperglycaemia, impaired glucose tolerance or diabetes mellitus are present in two-thirds of survivors.6

The Japanese with diabetes have 2-5 times risk for stroke than nondiabetic.5 The Japanese men risk of stroke in Hawaii increased with age for both diabetic and nondiabetic ones. The risk was substantially higher among diabetic compared with nondiabetic individuals at almost all ages.5 Women with diabetes mellitus and no history of CVD had a 3-fold–increased fatal stroke risk compared with nondiabetic women without CVD.6 Type 2 diabetes is an established risk factor in stroke, but the relationship between asymptomatic hyperglycaemia, hyperinsulinemia, and stroke incidence remains uncertain.4 It’s very important to screen the risk for stroke in diabetic patients, because the presence of DM is the most powerful determinant of SCI (Silent Cerebral Infarction) in hypertensive patients. Even in white coat hypertension, DM is a strong risk factor in multiple SCIs.9

The diabetic stroke patient was 3.2 years younger than the nondiabetic and suffered from hypertension more frequently. Diabetes influences stroke in several aspects: age, subtype, speed of recovery, and mortality. Increased glucose level upon admission independently increase mortality from stroke in nondiabetic but not in diabetic patients.11

**SCREENING FOR STROKE IN DIABETIC PATIENT**

How can we predict the incidence of stroke in diabetic patient in the future? United Kingdom Prospective Diabetes Study had launched a software of UKPDS Risk Engine in 2002. Variables included in
the final model were duration of diabetes, age, sex, smoking, systolic blood pressure, total cholesterol to high-density lipoprotein cholesterol ratio and presence of atrial fibrillation. Not included in the model were body mass index, hemoglobin A1c, ethnicity, and ex-smoking status. The use of the model is illustrated with a hypothetical study power calculation. Several limitations arise from the use of clinical trial rather than epidemiologic data, although they have attempted to correct for the impact of trial selection criteria, as has been described above. For time periods < 4 years or > 20 years after diagnosis of diabetes, or for ages > 65 at diagnosis of diabetes, prediction from this model is extrapolation. Definition of nonfatal stroke is more stringent than the definition that is used sometimes, requiring signs or symptoms to persist for more than a month. The model does not distinguish between fatal and nonfatal stroke or between ischemic and hemorrhagic stroke.12

Carotid bruit is the other modality to predict stroke in the future in diabetic patients. Type 2 diabetic patients found to have incidental carotid bruits have >6 times the risk of first stroke in the first 2 years than those without a bruit and should receive intensified management of vascular risk factors. Although auscultation of carotid bruit has been shown to be a reliable indicator of underlying arterial stenosis in symptomatic patients in the general population, the effectiveness of carotid auscultation in screening for under-lying arterial disease has been questioned, especially in asymptomatic patients. Further investigation is needed, such as carotid Doppler study in asymptomatic patients with type 2 diabetes who have detectable carotid bruit.13 Patients with a carotid artery stenosis, including those with an asymptomatic or moderate stenosis, have a considerable risk of ischemic stroke. Stiffness was assessed by measurement of distension of the common carotid arteries. The distension of an artery is the change in diameter in systole relative to diastolic diameter during the cardiac cycle. The increasing carotid stiffness is associated with a higher prevalence of previous TIA or ischemic stroke.14

QTc interval prolongation is a predictor of cardiovascular morbidity and mortality in general population and in patients with diabetes. QTc interval prolongation is a predictor of future stroke in patients with type 2 diabetes. QTc interval prolongation (≥ 470 ms12) was an independent predictor of stroke. Bazzet’s formula for QTc = QT x RR-1/2. Two potential confounders of QTc interval prolongation are heart rate disorders and the presence of conduction disturbances on ECG.15

Proteinuria (≥ 20 and < 200 µg/min) is an independent risk factor for cardiovascular disease in patients with type 2 diabetes mellitus. Type 2 diabetes patients with proteinuria will increase 3.23 times for stroke in the future. Albuminuria is a strong predictor of renal disease progression, premature death of cardiovascular origin, and foot ulcer in patients with type 2 diabetes. It may reflect a generalized vascular process that affects the glomeruli and intima of large vessels simultaneously. The relationship between microalbuminuria and cardiovascular disease mortality in patients with type 2 diabetes is well established.16

POSTSTROKE DIABETES

Given the “epidemic” of diabetes, with substantially increasing diabetes prevalence each year across all age-and race/ethnicity groups, the significance of diabetes as a risk factor for stroke is becoming more evident.5 Hyperglycaemia has been observed after acute stroke, and is associated with a poor prognosis. Hyperglycaemia seen after an acute stroke is secondary to a stress response and they do not support the theory of hyperglycaemia being harmful to ischaemic nervous tissue. These finding has implication to the treatment of acute stroke with hypoglycaemic agents.17

The majority of acute stroke patients have disorder of glucose metabolism, and in most cases this fact has
been unrecognized. Diabetes worsens the outcome of acute stroke. Therefore, in the post–acute phase, an oral glucose tolerance test should be recommended in all stroke patients with no prior history of diabetes. In the post–acute phase, 20.2% had previously known diabetes; 16.4% were classified as having newly diagnosed diabetes, 23.1% as having IGT, 0.8% as having impaired fasting glucose; and only 19.7% were normoglycemic. So, an OGTT screening in the post–acute phase has to be recommended in all stroke patients with no prior history of diabetes.6

Previously undiagnosed DM may be more prevalent than known DM in hospitalised patients with acute stroke. Performing an OGTT at 12 weeks post stroke provides an accurate measurement of the prevalence of DM and IGT in survivors and enables the results to be related to admission values for plasma glucose and HbA1c. This allows their value in predicting the presence of DM in acute stroke patients to be calculated. Admission hyperglycaemia (≥ 6.1 mmol/l) plus raised HbA1c concentration predicts unrecognized DM in acute stroke patients, with sensitivity of 86% and specificity of 94%. The development of type 2 diabetes is preceded by a prolonged period of insulin resistance with compensatory hyperinsulinemia and a gradual onset of hyperglycemia. Both hyperglycemia and hyperinsulinemia have been shown to be independently associated with increased risk of coronary heart disease (CHD). The role of hyperglycemia and hyperinsulinemia as risk factors for stroke is less well documented. Although some studies have shown hyperglycemia to be independently associated with risk of stroke in nondiabetics, the increased risk at higher levels of serum insulin was due in part to the men who developed diabetes in the follow-up period.4

**PATHOLOGY OF STROKE IN THE DIABETIC PATIENT**

Although diabetes is a strong risk factor for stroke, it is still unclear whether stroke subtype, severity, and prognosis are different between diabetic and nondiabetic patients. Stroke in diabetic patients has a specific clinical pattern and a poor prognosis in terms of motor function, which emphasizes the need for early diagnosis and treatment of every case of diabetes. Stroke in diabetic patients was different from stroke in nondiabetic patients from several perspectives. In diabetic stroke patients, the frequency of intracerebral hemorrhage was lower, the rate of lacunes was higher, recovery of handicap by Rankin Scale score was worse, and mortality was not increased.2 Intracerebral hemorrhages were six times less frequent in diabetic patients.11 Pathology type of stroke in diabetic patient confronted for nondiabetic regarding the European BIOMED Stroke Project lists in table 4.18

**Table 3. Summarised OGTT results in 61 survivors at 12 weeks post stroke**

<table>
<thead>
<tr>
<th>Plasma glucose &gt; 6.1 mmol/l</th>
<th>DM Present</th>
<th>DM Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ HbA1c &gt; 6.2%</td>
<td>12</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>+ HbA1c &lt; 6.2%</td>
<td>2</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>47</td>
<td>61</td>
</tr>
</tbody>
</table>

Sensitivity = 12/14 x 100 = 86%
Specificity = 44/47 x 100 = 94%

**Table 4. Pathology type of stroke in diabetic patient**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diabetes</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>77.5</td>
<td>71.9</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>8.5</td>
<td>11.5</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>0.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>7.3</td>
<td>6.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical syndromes of ischemic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACI*</td>
</tr>
<tr>
<td>PACI</td>
</tr>
<tr>
<td>POCl</td>
</tr>
<tr>
<td>LACI</td>
</tr>
<tr>
<td>N=432</td>
</tr>
<tr>
<td>N=1605</td>
</tr>
<tr>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**PREVENTING STROKE**

Preventing incidence of stroke in diabetic patients is started by identification followed by several interventions of modifiable risk factors, especially hypertension, cigarette smoking, high LDL cholesterol, diabetes mellitus, coronary heart disease, left ventricular hypertrophy, atrial fibrillation, and peripheral vascular disease, etc. Complete recommendation to modify risk factor according to American Heart Association is shown in table 5 and 6.

Controlling the blood pressure has been proven as an effective prevention of stroke both in diabetic or non-diabetic. In the *Systolic Hypertension in the Elderly trial*, the treatment effect (reduced risk of stroke) in the intervention compared to the control group was similar for diabetic and nondiabetic subjects. Complication of treatment also did not appear to vary between diabetic and nondiabetic individuals.3
Sulfonylurea, the group of commonly antidiabetic drug, was not associated with increased mortality or adverse clinical outcome in patients with diabetes and ischemic stroke. Despite concern regarding sulfonylurea because of increased mortality and impairment of ischemic preconditioning, glibenclamide and its derivatives seem to be safe and showed no impact on the immediate outcome after stroke.19

Antiplatelet aggregating agents such as aspirin are effective in decreasing the incidence of stroke,
especially among individuals with existing cardiovascular disease or transient ischemic attack. At least one study had shown beneficial effect in both diabetic and nondiabetic individuals. No difference between aspirin and warfarin in the prevention of recurrent ischemic stroke or death or in the rate of major hemorrhage. Consequently, we regard both warfarin and aspirin as reasonable therapeutic alternatives.

Smoking cessation will also decrease the risk of stroke. Statins may reduce the incidence of all strokes without any increase in hemorrhagic strokes, and this effect is mainly driven by the extent of between-group LDL-C reduction. Carotid IMT (intima-media thickness) progression is also strongly correlated with LDL-C reduction. Anti-hypertensive agents are used in lowering blood pressure for the prevention of vascular event in patients with previous stroke or transient ischemic attack. Vascular prevention is associated positively with the magnitude by which blood pressure is reduced.

**ENDARTHERECTOMY AND CAROTID STENTING**

Carotid angioplasty and stenting is minimally invasive revascularization that has become a popular and acceptable treatment option in the United States for high surgical risk patient with internal carotid artery atherosclerosis. It is effective and its risk profile is acceptable. Dynamic cerebral dysautoregulation in patient with severe carotid obstruction is readily and completely remedied by carotid recanalization by carotid stenting or endarterectomy, even the standard therapy for it is endarterectomy.

Carotid artery angioplasty and stent placement have recently emerged as an alternative to carotid endarterectomy for primary and secondary prevention of stroke related to carotid stenosis. Although initial outcome studies indicated higher morbidity and mortality rates for carotid artery angioplasty than carotid endarterectomy that is considered as an acceptable standard procedure, the development of new stent technologies and the advent of embolic cerebral protection devices have improved procedural safety and clinical outcomes. In-hospital outcomes with carotid stenting were similar to those with endarterectomy. Carotid stenting is less invasive than endarterectomy, but the risk for stroke and death as the side effect of endarterectomy are less frequent than carotid stenting. Cost and resource utilization with stenting were substantially less than those with endarterectomy. At 2 years, carotid stenting appeared not only durable but also effective in stroke prevention. But the benefit of vertebral artery revascularization has not yet become evidence.

| **Table 6. Recommendations for modifiable behavioral risk factors** |
|--------------------------|-----------------|-----------------|
| **Risk Factor**          | **Recommendation**                                                                 |
| Smoking                  | All ischemic stroke or TIA patients who have smoked in the past year should be strongly encouraged not to smoke. Avoid environmental smoke. Counseling, nicotine products, and oral smoking cessation medications have been found to be effective for smokers. |
| Alcohol                  | Patients with prior ischemic stroke or TIA who are heavy drinkers should eliminate or reduce their consumption of alcohol. Light to moderate levels of 2 drinks per day for men and 1 drink per day for nonpregnant women may be considered. |
| Obesity                  | Weight reduction may be considered for all overweight ischemic stroke or TIA patients to maintain the goal of a BMI of 18.5 to 24.9 kg/m2 and a waist circumference of <35 in for women and <40 in for men. Clinicians should encourage weight management through an appropriate balance of caloric intake, physical activity, and behavioral counseling. |
| Physical activity        | For those with ischemic stroke or TIA who are capable of engaging in physical activity, at least 30 minutes of moderate-intensity physical exercise most days may be considered to reduce risk factors and comorbid conditions that increase the likelihood of recurrence of stroke. For those with disability after ischemic stroke, a supervised therapeutic exercise regimen is recommended. |
|                          | **Class/Level of Evidence** | **Class/Level of Evidence** | **Class/Level of Evidence** |
|                          | Class I, Level C            | Class IIa, Level C       | Class IIb, Level C         | Class IIb, Level C   |

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Carotid stenosis >60-70% has very high risk for stroke when conventional medical therapy with only drug has been chosen. The benefit of pharmacological medication compared with endarterectomy is similar when carotid stenosis <60%. And in carotid stenosis <30%, medication without invasive surgical treatment is more beneficial.

CONCLUSION

Eventhough endarterectomy and carotid stenting have become a popular and acceptable treatment option, the risk and side effect of the procedure must be considered properly. The risk of any neurological events is still higher, particularly during catheterization and ballooning, the carotid stenting procedure showed higher risk than endarterectomy (7.9% : 2.3%, OR 5.2, 95% CI, p=0.001). Distal embolisation frequently followed carotid stenting and must be prevented. The risk, in addition to the potential risk of embolisation to distal sites, provide a rationale for early antiplatelet therapy concomitant with carotid artery stenting. The risk of late stent (>30 days after stenting) thrombosis in some patients, particularly those who receive drug-eluting stents, provide a rationale for prolonged antiplatelet prophylaxis against late atherothrombotic events. Because of the systemic and progressive of atherothrombosis, protection against ischemic vascular events in other arterial bed expands the benefit of long-term antiplatelet therapy.

REFERENCES