·Special Lectures·

Prevention of ischemic stroke in diabetic patients

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Keywords

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【关键词】 脑缺血； 卒中； 预防； 糖尿病

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Abstract

Diabetes can cause more than double risk of ischemic stroke and is associated with with poor long-term prognosis after ischemic stroke. Surprisingly, intensively treating hyperglycemia has not been shown to have beneficial outcomes in either primary or secondary prevention in stroke disease. Encouragingly, multifactorial management of risk factors of ischemic stroke, in particular, lifestyle, glucose concentration, hypertension, and dyslipidemia will prevent a substantial number of ischemic stroke and improve the prognosis in diabetic patients. Antithrombotic treatment and carotid surgery are also essential for primary and secondary stroke prevention in selected diabetic patients. Evidence for primary and secondary prevention of ischemic stroke in diabetic patients is steadily evolving, and it is imperative that clinicians are actively informed regarding the latest advance in order to better implement stroke prevention in diabetic patients.

【摘要】 糖尿病可使发生缺血性卒中的风险增加2倍以上，并且合并缺血性卒中的糖尿病患者长期预后不良。目前所采取的强力降血糖治疗并未使糖尿病患者从缺血性卒中的一级和二级预防中获益。然而，有研究显示，具有针对性的缺血性卒中危险因素管理，特别是对不良生活方式、血糖、高血压、脂质代谢紊乱的干预，可预防糖尿病患者缺血性卒中的发生，并改善预后。在符合干预标准的糖尿病患者中，抗血栓治疗和颈动脉外科手术对缺血性卒中的一级和二级预防是必要的。本文拟对近年公布的糖尿病患者缺血性卒中一级和二级预防的相关证据进行概述，使临床医师了解该领域的研究现状与动态，从而更好地实施糖尿病患者的卒中预防措施。

There are about 347 million people with diabetes all over the world, and ageing and population growth is likely to intensify this burden [1]. The type 1 and type 2 forms are the most typical. Type 1 diabetes accounts for 5-10% of total diabetes population [2], and type 2 diabetes accounts for 90% [3]. Diabetes and ischemic stroke are common disorders that often arise together. Diabetes is an important risk factor for ischemic stroke. Compared with individuals without diabetes, people with diabetes have more than double the risk of ischemic stroke after correction for other risk factors [4]. Of diabetic persons, the risk of stroke is higher in women (hazard ratio [*HR*], 2.8; 95% confidence interval [CI], 2.4-3.4) than in men (*HR*, 2.2; 95% CI, 1.8-2.5) [4]. Diabetes is associated with different subtypes of ischemic stroke, including lacunar, large artery occlusion, and thromboembolic strokes [5-7]. Moreover, the risk of atrial fibrillation, which is a major cause of thromboembolic stroke,increased by 40% in individuals with diabetes [8].

Stroke is the second leading cause of long-term disability in high - income countries and the second leading cause of death worldwide [9]. In China, with 1.4 billion population, stroke has exceeded heart disease to become the leading cause of death and disability in adults [10], with ischemic stroke being a predominant subtype [11]. Mortality more than 1 year after ischemic stroke was slightly increased (*HR*, 1.2; 95% CI, 1.1-1.2) in patients with diabetes compared with those without [12]. Furthermore, risk of recurrent stroke is

raised (*HR*, 1.8; 95% CI, 1.2-2.8) in diabetic patients [13], which could be even more striking in patients with diabetes younger than 50 years [14].

Thus, primary and secondary prevention of ischemic stroke in patients with diabetes should be very important for their clinical outcomes. The review aims to overview potentially modifiable risk factors and to objectively evaluate the effect assessment and treatment of associated risk factors on reducing the risk of stroke in patients with diabetes.

Diabetes-associated risk factors for stroke include not only lifestyle, vascular risk factors (glucose concentrations, hypertension, and dyslipidemia) and atrial fibrillation, but also genetic and demographic factors. Several risk factors are potentially modifiable, in particular lifestyle factors and vascular risk factors. Antithrombotic treatment and carotid surgery are also important preventing strategies of ischemic stroke in diabetic patients. The protocol of stroke prevention are showed in the following Table 1.

Lifestyle advices

Lifestyle probably has the largest effect on risk of stroke. Smoking, obesity, inactivity, excessive alcohol intake, and unhealthy diets should be strongly discouraged in people with diabetes. Lifestyle modification in this population is associated with a substantial decline in stroke incidence (*HR*, 0.62; 95% CI, 0.39-0.98) [15]. Moreover, modest weight loss (5-10% of bodyweight) in individuals with type 2 diabetes has been associated with substantial improvement of cardiovascular risk factors and glycaemic control [16-17]. Physical activity is an important part of the diabetes management plan. Regular exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being [18]. American Diabetes Association (ADA) suggests that adults with diabetes should be advised to perform at least 150 min/week of moderate-intensity aerobic physical activity (50-70% of maximum heart rate), spread over at least 3 d/week with no more than two consecutive days without exercise. In the absence of contraindications, adults with type 2 diabetes should be encouraged to perform resistance training at least twice per week [19].

Vascular risk factors management

Glucose-lowering treatment

Glycemic control is fundamental to the management of diabetes. However, two large long-term trials have compared the effects of intensive versus standard glycaemic control in participants at fairly high risk of stroke with longstanding type 2 diabetes. No difference in cardiovascular outcomes was reported with intensive glycaemic control [20-21]. In the Action to Control Cardio-vascular Risk in Diabetes (ACCORD) study [22], the glycaemic control study was terminated after 3.7 years owing to increased mortality in the intensive treatment group (HbA1c < 42 mmol/mol [6%]). Participants assigned to the intensive therapy group were subsequently switched to the standard control group (HbA1c 53-64 mmol/mol [7-7.9%]) and were followed up for about 1.2 years. Risk of non-fatal stroke was similar before and after the transition. Targeting intensive glycaemic control versus standard glycaemic control in type 2 diabetic patients did not reduce the risk of cardiovascular mortality (risk ratio [*RR*], 1.1; 95% CI, 0.90-1.3) or non-fatal stroke (*RR*, 0.96; 95% CI, 0.80-1.2) [23]. Risk of severe hypoglycaemia was increased significantly when intensive glycaemic control was targeted (*RR*, 2.0; 95% CI, 1.4-3.0) [23].

To date, no enough evidence is available to show that stroke prevention will be improved by intensive glucose-lowering treatment in people with either type 1 or type 2 diabetes. Lowering HbA1c to below or around 7% has been shown to reduce microvascular complications of diabetes and, if implemented soon after the diagnosis of diabetes, is associated with

Table 1. Ischemic stroke prevention in diabetes

Outlines of stroke prevention strategies
Discourage smoking, inactivity, excessive alcohol intake, and obesity.
Regulate blood glucose or HbA1c based on patients´ characteristics.
Regulate blood pressure < 140/80 mm Hg; ACEI or ARB are recommended as first-line treatment
Prescribe statins
Prescribe platelet-aggregation inhibitors in patients with clinically manifest vascular disease and sinus rhythm.
Apply the CHA_2DS_2-VAS score and prescribe warfarin in patients with clinically manifest vascular disease and with atrial fibrillation.
Undertake carotid surgery in patients with symptomatic high-grade carotid stenosis.
Undertake carotid surgery in patients with asymptomatic carotid stenosis and embolic signals.

ACEI: angiotensin-converting-enzyme inhibitors; ARB: angiotensin Ⅱ receptor blockers; CHA_2DS_2-VAS = congestive heart failure/left-ventricular dysfunction (1 point); hypertension (1); age ≥ 75 years (2); diabetes mellitus (1); stroke/transient ischmic attack/thromboembolism (2); vascular disease, ie, previous myocardial infarction/ peripheral artery disease/aortic plaque (1); age 65–74 years (1); female sex (1).

long-term reduction in macrovascular disease. So a reasonable HbA1c goal for many nonpregnant adults is < 7% [19]. More stringent HbA1c goal (such as < 6.5%) is appropriate for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effect of treatment. Appropriate patients might include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease (CVD) [19]. Conversely, less stringent HbA1c goals (such as < 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education (DSME), appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin [19]. Therefore, clinicians should balance risk of (recurrent) hypoglycemia against the advantages of a lower amount of HbA1c, taking into account patient's age, duration of diabetes, and comorbidities.

Hypertension

Hypertension is a common comorbidity of diabetes, affecting the majority of patients, and is a major risk factor for both CVD and microvascular complications. In patients with type 2 diabetes, lowering of blood pressure has a great effect on the risk of future stroke [24-25]. In secondary prevention, a Meta-analysis of seven randomized controlled trials showed that antihypertensive drugs reduced stroke recurrence after stroke or transient ischemic attack (TIA) (*RR*, 0.76; 95% CI, 0.63-0.92) [26]. Another Meta-analysis assessed the effects of blood pressure control (≤ 135 mm Hg vs 140 mm Hg). The results showed intensive BP control was associated with a 10% reduction in all-cause mortality (odd ratio [*OR*], 0.90; 95% CI, 0.83-0.98), a 17% reduction in strokes (*OR*, 0.83; 95% CI, 0.73-0.95), compared with standard treatment. This difference was mainly driven by systolic pressure of 130-135 mm Hg. Control of blood pressure below 130 mm Hg was associated with a greater reduction in stroke but a 40% increase in serious adverse events, with no benefit for cardiac, renal, and retinal outcomes [27].

Although previous opinion was a blood pressure of less than 130/80 mm Hg for patients with diabetes, now ADA suggests that people with diabetes and hypertension should be treated to a systolic blood pressure goal of < 140 mm Hg. Lower systolic targets, such as < 130 mm Hg, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden. It also suggest that patients with diabetes should be treated to a diastolic blood pressure < 80 mm Hg [19]. Hence, blood pressure should be lowered and monitored indefinitely after stroke or TIA in diabetic patients. However, blood pressure should not be lowered intensively in patients with suspected haemodynamic stroke or in those with symptomatic carotid or middle cerebral artery (MCA) stenosis.

As for treatment for hypertension, patients with a blood pressure > 120/80 mm Hg should be advised on lifestyle changes to reduce blood pressure. Patients with blood pressure ≥ 140/80 mm Hg should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve blood pressure goal [19]. The choice of antihypertensive drugs is probably less important than the target levels. Beta blockade type medications worsen glycaemia and had better be avoided. Currently, angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin Ⅱ receptor blockers (ARB) are typically recommended as first-line drugs for diabetic patients [19, 28]. Both of them have been demonstrated to preserve and improve renal function in hypertensive diabetic individuals. When using either of these drugs, it is important to titrate them up to the maximum tolerated dose, for their beneficial effect will be increased [29]. In pregnant patients with diabetes and chronic hypertension, blood pressure target goals of 110-129/65-79 mm Hg are suggested in the interest of long-term maternal health and minimizing impaired fetal growth. ACEI and ARBs are contraindicated during pregnancy [19].

Dyslipidemia

Lipid management is an established, effective approach to reduce CVD risk in diabetes. A daily dose of 40 mg simvastatin administered to 5963 patients with type 2 diabetes, of whom half did not have any evidence of arterial occlusive disease, was associated with a 28% (95% CI, 8-44) reduction in ischemic stroke, independent of baseline lipid levels [30]. In people with type 2 diabetes with no history of CVD, daily use of 10 mg atorvastatin was associated with a 37% (95% CI, 17-52) reduction in cardiovascular events and with a 48% (95% CI, 11-69) reduction in all types of stroke [31]. The combination of fenofibrate and simvastatin did not reduce the rate of fatal or non-fatal cardiovascular events more than simvastatin alone [32].

Lifestyle modification focusing on the reduction of saturated fat, trans fat, and cholesterol intake; increase of n-3 fatty acids, viscous fiber, and plant stanols/sterols; weight loss (if indicated); and increased physical activity should be recommended to improve the lipid profile in patients with diabetes [19]. Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, in all individuals with type 2 diabetes for secondary prevention and in most for primary prevention [19]. In diabetic individuals without overt stroke or TIA, the primary goal is an low-density lipoprotein (LDL) cholesterol < 100 mg/dl (2.6 mmol/L). In individuals with overt stroke or TIA, a lower LDL

cholesterol goal of < 70 mg/dl (1.8 mmol/L), using a high dose of a statin, is an option. If drug-treated patients do not reach the above targets on maximal tolerated statin therapy, a reduction in LDL cholesterol of 30-40% from baseline is an alternative therapeutic goal. Triglyceride levels < 150 mg/dl (1.7 mmol/L) and high-density lipoprotein (HDL) cholesterol > 40 mg/dl (1.0 mmol/L) in men and > 50 mg/dl (1.3 mmol/L) in women, are desirable. However, LDL cholesterol-targeted statin therapy remains the preferred strategy. Combination therapy has been shown not to provide additional cardiovascular benefit above statin therapy alone and is not generally recommended [19]. Statin therapy is contraindicated in pregnancy [19].

Antithrombotic treatment

Antiplatet therapy

Platelets from patients with type 1 and type 2 diabetes exhibit enhanced platelet aggregation activity and platelet sensitivity early in the disease course that may precede the development of CVD [33]. The importance of platelets in the athero-thrombotic process has led to investigation of using antiplatelet agents to reduce CVD risk. Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with previous myocardial infarction or stroke (secondary prevention). Its net benefit in primary prevention among patients with no previous cardiovascular events is more controversial, both for patients with and without a history of diabetes [34]. For the secondary prevention of stroke, the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial compared clopidogrel and aspirin in this population. This study enrolled people with a history of cardiovascular disease, one-third of which was stroke related. In a post hoc analysis they suggested that clopidogrel was better than aspirin for diabetic patients [35].

On the whole, whether antiplatelet treatment should be started or not depends on their 10-year cardiovascular risk in diabetic patients [19]. We should consider aspirin therapy (75-162 mg/d) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk > 10%). This includes most men > 50 y or women > 60 y who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia or albuminuria). Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk (10-year CVD risk < 5%, in men < 50 y and women < 60 y of age with no major additional CVD risk factors), since the potential adverse effects from bleeding probably offset the potential benefits. Clinical judgment should be used for those at intermediate risk (younger patients with one or more risk factors, or older patients with no risk factors; those with 10-year CVD risk of 5-10%) until further research is available. It is remarkable that use of aspirin in patients under the age of 21 is contraindicated due to the associated risk of Reye's syndrome. We should use aspirin therapy (75-162 mg/d) as a secondary prevention strategy in diabetic patients with a history of CVD. For patients with CVD and documented aspirin allergy, clopidogrel (75 mg/d) should be used. Currently, there is no evidence to suggest that a combination of aspirin and clopidogrel, even in high risk people, such as those with diabetes, has any therapeutic advantage and may actually be harmful for stroke prevention [36].

Anticoagulation therapy

Diabetes is not only a risk factor for atrial fibrillation [19], but also increases the risk of embolic complications in individuals with atrial fibrillation, as indicated by the CHA_2DS_2-VAS score (congestive heart failure or left-ventricular dysfunction [1 point]; hypertension [1]; age 75 y or older [2 points]; diabetes mellitus [1]; stroke, transient ischemic attack, or thromboembolism [2]; vascular disease (previous myocardial infarction, peripheral artery disease, or aortic plaque) [1]; age 65-74 y [1]; and female sex [1]) [37]. Therefore, patients with diabetes and atrial fibrillation should receive platelet aggregation inhibitors if they have none of the other risk factors included in CHA_2DS_2-VAS score and warfarin in all other cases [38]. Dabigatran, rivaroxaban, and apixaban are proven to protect patients with atrial fibrillation as well as or even better than warfarin, but the definite role of these new antithrombotic drugs in patients with a recent TIA or minor ischemic stroke remains to be established [39].

Carotid surgery

Carotid endarterectomy for secondary stroke prevention in patients with high-grade stenosis of the carotid artery is effective, but has not been investigated specifically in patients with diabetes. Both periprocedural and long-term risks are higher in individuals with diabetes than in those without [40-41], but this increased risk should not be a reason to withhold surgery in patients with diabetes and symptomatic high-grade carotid stenosis. On the other hand, detection of asymptomatic embolisation can be used to identify patients with asymptomatic carotid stenosis who are at a higher risk of stroke and TIA, patients with asymptomatic carotid stenosis and embolic signals are likely to benefit from carotid endarterectomy [42].

Conclusions

Intensive monitoring of vascular risk factors is important in the long term. Training programmes for patients aimed at acquiring the skills for a healthy

lifestyle and self-monitoring of blood glucose and blood pressure can be useful. Antithrombotic treatment and carotid surgery should be considered in selected diabetic patients.

Evidence for primary and secondary prevention of ischemic stroke in diabetic patients is steadily evolving, and it is important that clinicians are actively informed regarding the latest advance in order to better implement stroke prevention in diabetic patients.

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