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VASCULAR COGNITIVE IMPAIRMENT IN DIABETES MELLITUS: ARE PREVENTION AND TREATMENT EFFECTIVE?

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SUMMARY – Vascular dementia is caused by progressive atherosclerosis leading to multiple small strokes and subsequent brain damage. Approximately 10%-20% of all cases of dementia are attributed to vascular dementia. The 5-year survival rate is 39% for patients with vascular dementia compared with 75% for age-matched controls. It is a growing public health concern because of the lack of effective curative treatment options and rising global prevalence. Duration of diabetes mellitus of 10 years or longer, onset of diabetes before age 65, treatment with insulin and oral antidiabetic medications, and presence of diabetes complications have an impact on the incidence of vascular dementia. On the other hand, patients who suffered stroke either had or are later diagnosed with diabetes (16%-24%). Treatment of vascular dementia in diabetes patients rests on a two-pronged approach: modification of the underlying disease and prevention and treatment of dementia symptoms.

Key words: *Vascular dementia – prevention and control; Vascular dementia – therapy; Diabetes mellitus - complications*

Epidemiology

Vascular dementia is caused by progressive atherosclerosis leading to multiple small strokes and subsequent brain damage. Approximately 10%-20% of all cases of dementia are attributed to vascular dementia (immediately following Alzheimer's disease accounting for 60%-70% of all dementia patients). The 5-year survival rate is 39% for patients with vascular dementia compared with 75% for age-matched controls. It is a growing public health concern because of the lack of effective curative treatment options and rising global prevalence. The main subtypes of this disease are mild cognitive impairment, multi-infarct dementia, vascular dementia due to a strategic single infarct (affecting the thalamus, the anterior cerebral artery, the parietal lobes or the cingulate gyrus), vascular dementia due to hemorrhagic lesions, small vessel disease (which includes vascular dementia due to lacunar lesions and Binswanger's disease), mixed Alzheimer's and vascular dementia[1,2].

Common risk factors for this type of dementia are the same as for cerebrovascular disease and include unmodifiable risk factors of age, gender, race/ethnicity, genotype, previous myocardial infarction, transient ischemic attack (TIA) or stroke, and modifiable risk factors of diabetes, hyperlipidemia, arterial hypertension, atrial fibrillation, coronary and/or peripheral artery disease, obesity, physical inactivity, stress, alcohol consumption and smoking[2].

Association of Diabetes Mellitus and Dementia

Recent estimates on the prevalence of diabetes mellitus (DM, type 1 and type 2) have indicated diagnostic rates for adults over age 60 at 12%-20%. Approximately

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90% of these cases are type 2 diabetes. Studies have examined whether adverse cognitive effects of diabetes are broad or selective across domains. Verbal episodic memory is typically (but not uniformly) affected in diabetic patients. Diabetes related slowing has been observed with a variety of speed tasks, especially those measuring basic reaction time or perceptual speed, as well as executive functioning[2-6]. Association between DM and cognitive decline implies the following: duration of DM of 10 years or longer (odds ratio (OR) 1.76; 95%CI 1.16-2.68); onset of diabetes before age 65 (OR 2.20; 95%CI 1.29-3.73); treatment with insulin (OR 2.01; 95%CI 1.22-3.31); oral antidiabetic medications (OR 3.6; 95%CI 1.3-9.5); presence of diabetes complications (OR 1, 80; 95%CI 1.13-2.89); patients who suffered stroke either had or are later diagnosed with DM (16%-24%)[7,9].

Patients with diabetes are at a 1.5- to 3-fold risk of stroke compared with general population, and associated mortality and morbidity are greater than in those without this underlying condition. Even patients with a metabolic syndrome component have a 1.5-fold increased risk of stroke (Table 1)[7-11]. The Rotterdam study (6370 subjects) has shown that the diabetes attributable risk of vascular dementia is 8.8% (1.5-fold greater risk) and that lipoprotein associated phospholipase A2 (Lp-PLA2) is a new marker for atherosclerosis and cognitive decline[12].

The Kungsholmen project (1301 subjects) has shown a 2.6 (95%CI 1.2-1.6) hazard ratio for diabetic patients to develop vascular dementia. Hazard ratio was higher in diabetic patients with severe systolic hypertension or heart disease[13]. A Canadian study of health and aging (5574 subjects) has shown that DM is associated with vascular dementia (relative risk=2.03; 95%CI, 1.5-3.57)[14]. The Action to Control Cardiovascular risk in Diabetes-Memory in Diabetes (ACCORD-MIND; 2977 subjects) trial has shown that a 1% higher HbA_{1c} value was associated with significant 1.75 (95%, -1.22 to -2.28) point Digital Symbol Substitution Test (DSST) score, 0.20 (-0.11 to -0.28; p<0.0001) lower Mini Mental State Exam (MMSE) score, 0.11 point lower memory score (-0.02 to -0.19, p=0142) and worse score on the Stroop test (1.31-0.19, p=0.0094)[15].

The Longitudinal Aging Study Amsterdam (1183 subjects) and Honolulu Asia Aging study have shown that metabolic syndrome affects cognitive decline (p<0.05), especially in individuals with higher C-reactive protein and interleukin-6 values (inflammation) and higher glycemia values (hyperglycemia)[9]. A study on 7402 men has shown that body mass index values less than 20 and 22.5 or higher are associated with an increased risk of middle to old age diagnosis of dementia[9].

Genetic host contribution to blood vessel susceptibility to hypertensive damage was demonstrated in the NHLBI Twin Study (71% heritability for leukoaraiosis), as well as in the Framingham and GENOA studies. The Framingham Heart Study has shown stroke related genes on chromosome 4p (odds score 3.69) and chromosome 17 (odds score 1.78). COL4A1 gene was proved to have a role in small vessel disease[4-6].

Pathophysiology

The exact neuroanatomical or neurochemical effects of diabetes on cognitive performance are relatively unknown. Some studies suggest that frontal structures may be affected and may therefore be associated with deficits of episodic memory recall, verbal fluency, and executive functioning. Additionally, reduced volumes of the amygdale and the hippocampus in diabetes patients may underline deficits associated with learning and memory. Recent reports on magnetic resonance imaging abnormalities and cognitive changes found with white matter lesions and subcortical atrophy in type 2 diabetes patients suggest an accelerated rate of age-related structural changes. Other risk factors for cerebrovascular disease as comorbidities in diabetes patients may accelerate these structural changes and cognitive decline[1-4].

Generally, vascular complications of diabetes can be separated into microvascular (diabetic nephropathy, neuropathy and retinopathy) and macrovascular (coronary disease, cerebrovascular disease, peripheral artery disease) complications. These complications are primarily due to increased proatherogenic risk factors in diabetic patients, i.e. abnormal plasma lipid profiles, hypertension, and hyperglycemia. However, other pathological features associated with diabetes, such as insulin resistance and hyperinsulinemia, also lead to atherosclerotic changes in extracranial and intracranial vessels independently of glycemia or other

attendant risk factors. This is particularly expressed in smaller cerebral vessels increasing the incidence of both overt and silent lacunar infarctions. The central pathomorphological mechanism in these complications is atherosclerosis which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral, coronary or cerebrovascular system. In response to endothelial injury and inflammation, oxidized lipids from low density lipoprotein (LDL) particles accumulate in the endothelial part of the vessel wall. Angiotensin II may promote the oxidation of such particles. Monocytes then infiltrate the arterial wall and differentiate into macrophages, which accumulate oxidized lipids to form foam cells. Once formed, foam cells stimulate macrophage proliferation and attraction of T-lymphocytes. T-lymphocytes, in turn, induce smooth muscle proliferation in the arterial wall and collagen accumulation. The net result of the process is the formation of a lipid-rich atherosclerotic lesion with a fibrous cap. Rupture of this lesion leads to acute vascular infarction; these ruptures and bleeding into the plaque are more frequent in diabetic patients (diabetic patients have a higher perioperative risk of carotid endarterectomy as well). In addition to atheroma formation, there is strong evidence for increased platelet adhesion, hypercoagulability, impaired nitric oxide generation and increased free radical formation, as well as altered calcium regulation in diabetic patients[4-16].

Differential Diagnosis

The onset of vascular dementia goes unnoticed in the early stages; sometimes symptoms such as cognitive and intellectual impairment as well as carrying out everyday activities may become apparent only in the mid-to-late stages. The symptoms of dementia include memory loss, confusion, forgetfulness, poor concentration, inability to cope with everyday activities, language impairment, slurred speech, inability to follow simple instructions, laughing and crying inappropriately, behavioral changes, impaired social skills, eating problems, a shuffling or jerky gait, incontinence and/or lack of bowel control. Lateralizing signs such as hemiparesis, bradykinesia, hyperreflexia, ataxia, pseudobulbar palsy, and gait and swallowing difficulties may also be observed[1,4,9].

Several specific diagnostic criteria can be used to diagnose vascular dementia, as follows: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria; International Classification of Diseases, Tenth Edition criteria; National Institute of Neurological Disorders and Stroke – Association International pour la Recherché et L'Enseignement en Neurosciences (NINDS-AIREN) criteria; The Alzheimer's Disease Diagnostic and Treatment Center criteria; and the Hachinski ischemic score[3,4].

Prevention and Treatment

Treatment of vascular dementia in diabetes patients rests on a two-pronged approach: modification of the underlying disease and prevention and treatment of dementia symptoms. These include intensive glucose control (HbA_{1c} ≤7 mmol/L) with diabetic diet, oral antidiabetic agents or insulin, particularly when instituted early in diabetes patients, and delay or prevent clinically manifest cognitive changes. There is still no cure for vascular dementia, as pharmacotherapy can only treat the symptoms and control underlying modifiable risk factors[14].

The goals of pharmacotherapy should be as follows: primary and secondary prevention of cognitive changes in diabetes patients; reduction of the existing cognitive changes with acceptable pharmacotherapy side effects; restoration/improvement in functional measures and quality of life[14].

Various potential risk or preventive factors for vascular dementia have been suggested by epidemiological research: lifestyle changes including diet, physical activity and stress reduction, as well as pharmacological strategies such as antihypertensive drugs, statins, antiplatelet and anticoagulant therapy, antidiabetic drugs, insulin, hormone replacement therapy, nonsteroidal antiinflammatory drugs (NSAID), Ginkgo biloba, ENADPH, donepezil, galantamine, memantine, rivastigmine, cyclandelate, hydergine, pentoxifylline, and CDP choline.

Glycemic control has a high impact on vascular remodeling. The Insulin Resistance Atherosclerosis Study (IRAS) has shown that diabetes and glucose intolerance are independent risk factors connected with

an increase in the intima media thickness (IMT)[17]. The SANDS trial (The Stop Atherosclerosis in Native Diabetics Study) has shown that reduction in other cerebrovascular risk factors (hypertension, hyperlipoproteinemia) can slower progression of IMT thickening in diabetic patients[18].

Polyvitamin and antioxidant intake as well as diet are important in the treatment of vascular dementia. The Folic Acid and Carotid IMT (FACIT) study has shown that folic acid supplementation has beneficial effect on global cognitive functions[19]. Meta-analyses have shown that the intake of vitamin B6, vitamin B12, folate, antioxidants (vitamin C and E, beta-carotene, flavonoids, selenium and other), reduction of homocysteine levels in plasma, as well as the intake of polyunsaturated fatty acids, Mediterranean diet and physical activity decrease the risk of cognitive decline[20].

Blood pressure control is important in diabetic patients in order to prevent progression of vascular remodeling. The United Kingdom Prospective Diabetes Study (UKPDS) has shown that reduction of blood pressure (144/82 mm Hg) reduces the risk of cerebrovascular disease by 44% *versus* controls (154/88 mm Hg)[21,22]. The Heart Outcomes Prevention Evaluation (HOPE) and Perindopril Protection Against Recurrent Stroke Therapy (PROGRESS) studies have shown that angiotensin-converting enzyme (ACE) inhibitors reduce stroke incidence[9,23]. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study has shown reduction in stroke incidence in patients taking angiotensin receptor blockers[24]. The Anti hypertensive and Lipid lowering Treatment to Prevent Heart Attack Trial (ALLAHAT) confirmed previous results in diabetic patients with hypertension[15]. The Honolulu Asia Aging Study and Cache Country study suggest that antihypertensive therapy may reduce the risk of dementia and cognitive decline in diabetic patients without previous stroke[9,25]. The Study on Cognition and Prognosis in Elderly (SCOPE) has shown that specifically calcium channel blockers and ACE inhibitors have greatest effect in reduction of cognitive decline[26].

Table 1. Stroke subtypes in diabetic patients

Stroke	Diabetic patients	Nondiabetic patients
Ischemic/hemorrhagic	10 : 1	5 : 1
Stroke risk at age 55<	Increased	Low
Relative risk women/men	Women >men	Women <men
Infratentorial stroke	Frequent	Infrequent
Lacunar stroke	Frequent	Infrequent
Lesion volume	No difference	

Statin therapy has also an important role in the prevention and treatment of vascular dementia in diabetic patients. The Heart Protection Study (HPS; 5963 diabetic patients, 40 mg simvastatin *per* day) has shown a stroke risk reduction by 24%; the Collaborative Atorvastatin Diabetes study has shown a stroke risk reduction by 48% during 3.9 years[27-31]; the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study has shown a stroke risk reduction by 10% during 5 years; and the Fenofibrate Intervention and Event Lowering in Diabetes study has shown similar results[9,32]. Meta-analyses have shown that the adjusted relative risk of developing dementia in diabetic patients taking statins is 0.29 (0.13-0.63; p=0.002) *versus* non-treated individuals (OR 0.79; 95%CI 0.45-1.41)[9,27-31].

Antiaggregation therapy was proven as a good choice in the prevention of vascular incidents in diabetic patients. In the Clopidogrel *versus* Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study, aspirin 75-250 mg was proven as the best choice for primary and secondary stroke prevention in diabetic patients; in case of intolerance or resistance (about 1/5 of diabetic patients), clopidogrel 75 mg *per* day can be introduced[9]. According to the European Stroke Prevention Study (ESPS), a combination of aspirin and dipyridamole should be introduced in diabetic patients with recurrent strokes[7]. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) study did not show any better effect of taking a combination of aspirin and clopidogrel *versus* either of these medicines as monotherapy[33]. The Management of Atherothrombosis with Clopidogrel in High-risk patients with recent TIA or ischemic stroke (MATCH) study included 7599 patients, 68% of them diabetics[34]. Meta-analyses have shown that long-term use of NSAID reduces the risk of dementia, whereby the type of NSAID is important; the best choice is acetylsalicylic acid in low concentrations (75-100 mg).

Ginkgo biloba has been proven useful in secondary prevention of cognitive decline[4,9,35,36].

Anticoagulant therapy is recommended in diabetic patients with atrial fibrillation. The Warfarin-Aspirin ReInfarction Study II (WARIS II) has shown that aspirin is better than warfarin in stroke risk reduction in diabetic patients with recurrent strokes[37].

Long-term plasma glucose control is one of the main principles of diabetic treatment, as well as in the prevention of vascular complications.

The United Kingdom Prospective Diabetes Study (UKPDS) has shown the importance of lifestyle modification and appropriate diabetic therapy in stroke risk reduction, i.e. reduction of HbA_{1c} by 1% reduces stroke risk by 4%[22]. Tight control of glucose is important in primary and secondary prevention of cognitive decline, in type 2 diabetes (metformin monotherapy or add-on therapy with rosiglitazone or glyburide) and type 1 diabetes (Diabetes Control and Complications study, DCCT)[38].

In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP NIDDM) conducted in diabetic patients taking acarbose there was a very low stroke incidence (2/682 patients)[39]. In the Observational study/Diabetes Control and Complications, intensive insulin treatment reduced the rate of any vascular incident by 41%[38]. In the PROspective pioglitAzone Clinial Trial in macroVascular Events)-double blinded randomized study (PROACTIVE) including 5238 patients taking 45 mg pioglitazone *vs.* placebo over 34.5 months), pioglitazone reduced the risk of stroke in type 2 diabetic patients at a high risk of stroke[40]. Acute glycemic control is of great importance in patients with vascular incident. Meta-analyses of 32 studies have shown that hyperglycemia at admission (6-8 mmol/L) is a predictor of worse functional outcome, and increased 28-day mortality in previously nondiabetic patients (RR 3.1; 95%CI 2.5-3.8) as well in diabetic patients (RR 1.3; 95%CI 0.5-3.4)[9]. The Glucose Insulin in Stroke Trial-Pilot (GIST), Insulin in Acute Ischemic stroke (INSULINFARCT) and Insulin Resistance Intervention after Stroke Trial (IRIS) have shown that there are no differences in acute stroke treatment in diabetic patients; of great importance is regulation of all metabolic parameters, as well as of blood glucose concentration[9,38,41].

The aim of the treatment of cognitive decline changes is to improve neuronal cell metabolism (oxygen supply, microcirculation) and cholinergic neurotransmission. Cholinesterase inhibitors, which include donepezil, rivastigmine, memantine and galantamine, have proven symptomatic efficacy in Alzheimer's disease and may also have a role in the treatment of vascular dementia according to the findings of limited studies. Presently, their use may have some justification given the prevalence of dementia with mixed pathology. Vasodilators (e.g., hydergine, other alkaloids and cyclandelate) have some positive neuroprotective effect. Modest gains in cognition have been reported with hemorheological agents (pentoxifylline and propentofylline). Calcium channel blockers, ENADPH, vinca alkaloids, nootropics,

Table 2. Strategies for prevention of vascular dementia in patients with diabetes mellitus

1. Treat diabetes optimally
2. Treat hypertension optimally
3. Control hyperlipidemia
4. Persuade patients to cease smoking and decrease alcohol intake
5. Prescribe anticoagulants for atrial fibrillation
6. Provide antiplatelet therapy for high risk patients
7. Perform carotid endarterectomy for severe (>70%) carotid stenosis
8. Use dietary control for diabetes, obesity and hyperlipidemia
9. Recommend lifestyle changes (e.g., weight loss, exercise, reduce stress, decrease salt intake)
10. Intervene early for stroke and transient ischemic attacks with neuroprotective agents (e.g., propentofylline, calcium channel antagonists, N-methyl-D-aspartate receptor antagonists, antioxidants)
11. Provide intensive rehabilitation after stroke

and extracts of Ginkgo biloba may improve memory in vascular dementia patients[42-44]. A summary of the main strategies in the prevention and treatment is shown Table 2.

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Sažetak

VASKULARNI KOGNITIVNI POREMEĆAJ U ŠEĆERNOJ BOLESTI: JESU LI PREVENCIJA I LIJEČENJE UČINKOVITI?

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Vaskularna demencija nastaje kao posljedica progresivne aterosklerotske bolesti malih krvnih žila mozga uz posljedične višestruke manje moždane udare i oštećenje moždanog parenhima. Oko 10%-20% slučajeva demencije pripisuje se vaskularnoj demenciji. Preživljenje bolesnika s vaskularnom demencijom znatno je smanjeno (39%) unutar 5 godina u usporedbi s kontrolnom skupinom standardiziranom prema dobi. Dokazana je povezanost šećerne bolesti i kognitivnog propadanja u bolesnika sa šećernom bolesti koja traje 10 godina i duže, naročito u slučaju pojavnosti dijabetesa prije 65. godine života, liječenja inzulinom ili oralnom antidijabetičkom terapijom te prisutnosti komplikacija dijabetesa. Također u bolesnika koji su preboljeli moždani udar postoji povećana pojavnost prethodno ili tijekom hospitalizacije postavljene dijagnoze šećerne bolesti (16%-24%). Liječenje bolesnika s vaskularnom demencijom i šećernom bolesti počiva na dva dugoročna načela: modifikacija šećerne bolesti te prevencija i liječenje simptoma demencije.

Ključne riječi: *Vaskularna demencija – prevencija i kontrola; Vaskularna demencija – terapija; Šećerna bolest - komplikacije*