HYPERTRIGLYCERIDEMIA AS A POSSIBLE INDEPENDENT RISK FACTOR FOR STROKE

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SUMMARY – There are no reliable data on the relationship between ischemic stroke and elevated triglyceride levels. Results of previous studies have shown that elevated total cholesterol, high low-density lipoprotein cholesterol (LDL-C) and low high-density lipoprotein cholesterol (HDL-C) are modifiable risk factors for ischemic stroke. Recent evidence suggests that hypertriglyceridemia correlates with an increased risk of cardiovascular disease, particularly if the levels of HDL cholesterol are low and the levels of LDL cholesterol are high. The role of hypertriglyceridemia as an independent risk factor for stroke remains questionable, although correlation between elevated triglycerides and recurrent ischemic stroke has been established. Hypertriglyceridemia is an essential feature of metabolic syndrome, the most important risk factor for atherosclerosis and prothrombotic state, and both correlate with the increased risk of stroke. Lowering triglyceride levels might have a positive effect in stroke risk reduction. Efficacy of gemfibrozil was demonstrated in secondary stroke prevention in patients with coronary heart disease and elevated triglyceride levels. Fibrate derivatives might be utilized in primary stroke prevention, but their efficacy has not yet been established. There is substantial evidence to conclude that hypertriglyceridemia might be an independent risk factor for stroke, but additional studies are mandatory to confirm this presumption.

Key words: Hypertriglyceridemia; Risk factors; Stroke - control and prevention

Introduction

The possible role of hypertriglyceridemia as a possible risk factor for ischemic stroke remains controversial. However, a growing body of evidence indicates that hypertriglyceridemia is associated with atherosclerosis, endothelial dysfunction and prothrombotic state that may contribute to an increased risk of ischemic stroke. Recent evidence indicates that hypertriglyceridemia may correlate with an increased risk of cardiovascular events, particularly if high-density lipoprotein cholesterol (HDL-C) is low and low-density lipoprotein cholesterol (LDL-

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C) is high, or both¹⁻³. According to the Third Report of the National Cholesterol Educational Program and the Adult Treatment Panel (NCEP-ATP III), hypertriglyceridemia is classified at the following values: normal (1.7 mmol/L); borderline-high (1.7-2.2 mmol/L); high (2.2-5.6 mmol/L); and very high $(\geq 5.6 \text{ mmol/L})^4$. The atherogenic lipoprotein profile might be accentuated by the mutations of lipoprotein lipase, which plays an important role in degradation of triglycerides and synthesis of precursors of HDL-C particles⁵. Elevated serum levels of total cholesterol and LDL, along with low levels of HDL are recognized but modifiable risk factors for ischemic stroke. However, there are no reliable data on the relationship of ischemic stroke and elevated triglycerides in serum, thus there is no consensus on the importance of hypertriglyceridemia as an independent risk factor for ischemic stroke.

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Hypertriglyceridemia and the Possible Mechanisms of Ischemic Stroke

Atherosclerosis and thrombosis are credible mechanisms by which hypertriglyceridemia might cause ischemic stroke. Recent data show that postprandial hypertriglyceridemia in diabetic patients affects endothelial dysfunction by disturbing the mechanism of vasodilatation and promoting oxidative stress⁶. Correlation of hypertriglyceridemia and increased inflammatory markers in systemic inflammation, especially C-reactive protein, increases the risk of cardiovascular events, particularly for the coronary heart disease⁷⁻⁹. Numerous studies have shown that carotid intimamedia thickness (CIMT) is a reliable indicator of early atherosclerosis that is also associated with elevation of inflammatory markers, fibrinogen and circulating adhesion molecules, each individually being related to hypertriglyceridemia. Prothrombotic state is associated with hypertension and dyslipidemia, both having a significant effect on CIMT, particularly in the elderly¹⁰. In the Framingham Heart Study, triglyceride levels before meal were not associated with carotid atherosclerosis but the association of postprandial hypertriglyceridemia and CIMT was confirmed in subjects with type 2 diabetes^{11,12}. Hypertriglyceridemia induces cerebrovascular events by the mechanism of thrombosis, due to changes in coagulation cascade and by increasing plasma viscosity. Elevated fibrinogen is a strong and independent risk factor that is associated with progression of carotid disease and consequent vascular events¹³. Elevated levels of triglycerides, fibrinogen, total protein, LDL-C and total cholesterol are independently and positively correlated with increased plasma viscosity¹⁴. Hyperviscosity may lead to tissue ischemia due to disturbance of microcirculation and endothelial dysfunction, thus increasing the risk of thrombosis and promoting stroke¹⁵.

Triglycerides and Metabolic Syndrome

Hypertriglyceridemia is an important part of metabolic syndrome, which significantly increases the risk of cardiovascular and vascular events. Features of metabolic syndrome, defined by ATP III and World Health Organization, include abdominal obesity (waist circumference), HDL-C levels (<2.2 mmmol/L in men and <2.8 mmol/L in women), hypertension (>130/85 mmHg), pre-meal glucose levels (>6.1 mmol/L) and triglyceride levels (>1.7 mmol/L)⁴. Metabolic syndrome is associated with myocardial infarction and stroke, but the role of hypertriglyceridemia in metabolic syndrome as an independent risk factor for stroke is not entirely clear. Metabolic syndrome with pronounced dyslipidemia is the most important risk factor for atherosclerosis. It is associated with prothrombotic state and hyperinsulinemia, which further affects platelet function, coagulation and fibrinolysis^{16,17}. Patients with poorly controlled diabetes have higher triglyceride levels than those who are well controlled. Postprandial hyperlipidemia and exposure to atherogenic particles is prolonged in diabetic patients, thus subjects with diabetes and hypertriglyceridemia have increased mortality mostly due to coronary heart disease, which is particularly pronounced in middleaged men^{18,19}. Subjects with metabolic syndrome had a higher risk of stroke, ischemic heart disease and diabetes. When analyzed separately, hypertension was significantly associated with stroke, ischemic heart disease and diabetes, while hypertriglyceridemia and hyperglycemia were significantly associated only with ischemic heart disease and diabetes²⁰.

Triglycerides and the Risk of Stroke

Several studies have indicated that elevated triglycerides are not an independent risk factor for ischemic stroke^{21,22}. The Atherosclerosis Risk in Communities (ARIC) study showed weak and inconsistent correlation of triglyceride levels and ischemic stroke. Subjects without clinically manifest cardiovascular disease were included and results of the study showed no significant association between ischemic stroke and elevated lipid levels²³. Studies conducted in the elderly showed that triglyceride levels were not a significant risk factor for ischemic stroke or transient ischemic attack (TIA)^{24,25}. Results of some other studies have confirmed positive correlation between hypertriglyceridemia and ischemic stroke. The Blood Lipids and First-Ever Ischemic Stroke/Transient Ischemic Attack in the Bezafibrate Prevention study (BIP) showed that hypertriglyceridemia was an independent risk factor for ischemic stroke or TIA in patients with coronary heart disease²⁶. A meta-analysis conducted by the Asia-Pacific Cohort Studies Collaboration (APCSC) showed significant correlation of serum triglycerides

and fatal and non-fatal combined ischemic stroke, independently of other risk factors²⁷. Significant correlation of triglyceride levels and stroke was found in women in comparison with men for each triglyceride level increase²⁸. The Copenhagen City Heart Study showed strong linear association between triglyceride levels and relative risk of ischemic events (ischemic stroke or TIA) for each triglyceride level increase²⁹.

Hypertriglyceridemia and Ischemic Stroke Subtypes

Association of hypertriglyceridemia and different ischemic stroke subtypes is not utterly clear. Several studies have addressed lipid profile in different subtypes of ischemic stroke. Cardiovascular events were caused by cardio emboli in 48% of patients with increased triglyceride levels and atherosclerotic artery disease of large and small arteries^{30,31}. Metabolic syndrome was significantly associated with silent brain infarcts, particularly in middle-aged patients without previous history and clinical symptoms of stroke³². Significant correlation of metabolic syndrome and silent brain infarction, periventricular and subcortical white matter lesions was also detected in apparently healthy subjects³³. According to the components of metabolic syndrome, hypertension was associated with all types of lesions, while dyslipidemia and hyperglycemia were associated with subcortical white matter lesions and periventricular hyperintensities. Metabolic syndrome was associated with the prevalence of stroke independently of other risk factors, and synergistic effect of metabolic syndrome components was associated with the prevalence of silent brain infarcts³³. Silent brain infarct might announce clinically manifest stroke or dementia. A study conducted in apparently healthy subjects showed that more than 5% of cases had more than one lacunar ischemic lesion on magnetic resonance imaging³⁴. Age was significantly associated with the prevalence of silent stroke, while coronary heart disease and metabolic syndrome, particularly hypertension and hyperglycemia were associated with an increased risk of silent brain infarcts. A study conducted in neurologically healthy but elderly subjects showed that 15.7% of them had one or more ischemic lacunar lesions on magnetic resonance image, which corresponded to silent brain infarct. Hence, age and metabolic syndrome significantly correlated with the prevalence of silent brain infarct in apparently healthy older adults. According to the distribution of metabolic syndrome components, hypertension showed strongest correlation with silent brain infarcts. Positive trend between the number of metabolic components and silent brain infarct might serve as a diagnostic tool for prediction and prevention of stroke³⁵.

Efficacy of Lowering Triglyceride Levels

The Helsinki Heart Study has shown the efficacy of gemfibrozil in reducing triglyceride levels in patients with high basal triglyceride values by 43%, with greatest effect on coronary heart disease reduction. Lowering triglycerides might have a positive effect in stroke risk reduction, although it is not clear whether it is independently related to relative stroke risk reduction or relative coronary heart disease risk reduction³⁶.The Greek Atorvastatin and Coronary Heart Disease Evaluation Study (GREACE) was a randomized study, which included patients with coronary heart disease. Atorvastatin reduced triglycerides by 31% and LDL-C level by 46%, and significant reduction was observed in mortality and stroke rates. In atorvastatin group, the relative stroke risk reduction was 47%. Although the reduction of stroke was very dramatic, multivariate analysis was not conducted, so it cannot be concluded whether the results arose from reduction in triglycerides, LDL-C levels or neuroprotective properties of atorvastatin³⁷. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) compared gemfibrozil with placebo in men with coronary heart disease³⁸. Gemfibrozil was associated with significant relative risk reduction for TIA and carotid endarterectomy, reducing average triglyceride values by 31%. In later analysis of published VA-HIT studies, the relative risk reduction for ischemic stroke was highest in subjects with low HDL-C levels. The relative risk reduction for ischemic stroke was 28% in patients with triglyceride level 1.7 mmol/L and 21% in patients with triglyceride levels >1.7 mmol/L. Results of VA-HIT and consequent analysis suggest that gemfibrozil can reduce the incidence of TIA and stroke in men with coronary heart disease and low HDL-C^{38,39}. Gemfibrozil might reduce the risk of TIA and stroke due to its anti-inflammatory properties, which include stabilization of atherosclerotic plaques, reduction of factor VII, thrombin and platelet reactivity³⁸. Although it seems likely that triglyceride reduction in GREACE and VA-HIT contributed to the reduction of stroke, the effect of other factors cannot be excluded.

Conclusion

Current evidence suggests that hypertriglyceridemia correlates with an increased risk of cardiovascular diseases, particularly if serum level of HDL cholesterol is low⁴⁰. The role of hypertriglyceridemia as an independent risk factor for stroke remains questionable, although correlation between elevated triglycerides and recurrent ischemic stroke has been established. According to available data, we conclude that there is substantial scientific evidence to presume that hypertriglyceridemia might be an independent risk factor for stroke, but additional studies are required to confirm this presumption.

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Sažetak

HIPERTRIGLICERIDEMIJA KAO MOGUĆI NEZAVISNI ČIMBENIK RIZIKA ZA MOŽDANI UDAR

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Nema pouzdanih podataka o povezanosti ishemijskog moždanog udara i povišene razine triglicerida u serumu. Modificirajući čimbenici rizika za ishemijski moždani udar uključuju povišeni ukupni kolesterol, povišeni LDL te niski HDL kolesterol. Uloga hipertrigliceridemije kao nezavisnog čimbenika rizika za nastanak moždanog udara je upitna, iako rezultati novijih istraživanja upućuju na to da hipertrigliceridemija korelira s povećanim rizikom za kardiovaskularne bolesti, osobito ako je koncentracija HDL kolesterola niska, a LDL kolesterola povišena. Hipertrigliceridemija je ključna sastavnica metaboličkog sindroma, najvažnijeg čimbenika rizika za aterosklerozu i protrombozu koje su povezane s povećanim rizikom za nastanak moždanog udara. Snižavanje povišenih triglicerida može imati pozitivan učinak u smanjenju rizika za moždani udar. Rezultati studija su pokazali djelotvornost gemfibrozila u smanjenju kardiovaskularnih događaja u bolesnika s koronarnom bolesti srca i povišenim trigliceridima te u sekundarnoj prevenciji moždanog udara. Fibrati se primjenjuju u primarnoj prevenciji moždanog udara u bolesnika s hipertrigliceridemijom, ali njihova učinkovitost nije dokazana. Brojni dokazi upućuju na to da bi hipertrigliceridemija mogla biti nezavisan čimbenik rizika za moždani udar, ali za potvrdu ove pretpostavke potrebna su daljnja istraživanja.

Ključne riječi: Hipertrigliceridemija; Rizični čimbenici; Moždani udar – prevencija i kontrola