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Lipids and their effects on stroke

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Abstract

Stroke is a leading cause of death and disability worldwide with more than 4 million individuals suffering from stroke every year. The principal risk factors for stroke are age, race, gender, hypertension, smoking, diabetes and obesity. Recently the important role of lipids in the prevention of strokes has been identified. Similarly, there is evidence in favour of lipid lowering therapy (LLT), to prevent stroke. Lipoproteins are divided into five major classes (which are further sub-divided), based on density, composition, and electrophoretic mobility, namely chylomicrons, very low-density lipoproteins (VLDLs) intermediate-density lipoproteins (IDLs), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs). Elevated plasma LDL leads to infiltration of native LDL-C particles through the endothelium into intimal layer of arterial wall which leads to oxidation of macrophages into foam cells which lead to atherosclerotic lesions which on dispatch leads to embolism and which eventually can end up into embolic stroke. This review is intended to highlight the role of plasma lipids in the pathogenesis of stroke, and role of their ion in the prevention of stroke.

Keywords: CHD, LLT, VLDL, HDL.

Introduction

Stroke is a leading cause of death and disability worldwide with more than 4 million individuals suffering from stroke each year. Several conditions and lifestyle factors have been well established as risk factors for stroke. The principal risk factors for stroke are age, race, gender, hyper tension, smoking, diabetes, obesity, pre-existing coronary heart disease (CHD), and

atrial fibrillation. Atheroma lies at the root of the pathogenesis of thromboembolic stroke, extending from the diseased heart, through the atheromatous aorta and carotids to the intracranial circulation. It is therefore to be expected that dyslipidemia should contribute to the constellation of risk factors for this disease. Surprisingly this relationship is not so clear-cut, as with CHD, where it has unequivocally been shown to be associated. However, recently the important role of lipids in the prevention of strokes has been identified. Similarly, there is evidence in favour of lipid lowering therapy (LLT), to prevent stroke. This review is intended to highlight the role of plasma lipids in the pathogenesis of stroke, and role of their ion in the prevention of stroke.

Lipid metabolism

Lipoproteins are spherical particles with phospholipids, free cholesterol and protein making up the surface and a core consisting of mostly triglyceride and cholesterol ester. Lipoprotein particles are responsible for the transport of cholesterol and triglycerides in the blood stream. Apolipoproteins, which are the proteins on the surface, play a crucial role in regulating their transport and metabolism. Lipoproteins are divided into five major classes (which are further sub-divided), based on density, composition, and electro phoretic mobility, namely chylomicrons, very low-density lipoproteins (VLDLs) intermediate - density lipoproteins (IDLs), low - density lipoproteins (LDLs), and high -density lipoproteins (HDLs). The chylomicrons transport triglycerides of dietary origin from the small intestine into the plasma, whereas VLDL transports endogenously synthesized triglyceride which comes mainly from liver. HDL is subdivided into HDL2 and 3 and HDL carries cholesterol back from tissues to liver by the process of reverse cholesterol transport for its excretion into the bile.

Hypothesis of Atherogenesis

- Elevated plasma LDL leads to infiltration of native LDL-C particles through the endothelium into intimal layer of arterial wall.
- LDL-C particles are then oxidized
- Macrophages in the intima ingest oxidized LDL-C "foam cells" (foam cells are the early atherosclerotic lesion)
- Formation of advanced lesions > > fissures > > platelet aggregation > > thrombin generation > > fibrin formation > > thrombus and occlusion.

Endothelial cells express glycoproteins allowing monocyte adhesion to endothelial surface. Oxidized LDL-C stimulates endothelial cells to produce chemotactic factors and the cytokines more monocytes enter the intima and differentiate into macrophages. Macrophages produce growth factor smooth muscle cell proliferation fatty streak.

Prevalence of lipid disorders

In most series, about 80% of strokes are classified as ischaemic and the majority of these are secondary to an atherothrombotic mechanism. Cardiac embolism to the brain occupies a distant second place. It is estimated that more than 100 million Americans have a total blood cholesterol level equal to or higher than 200 mg/dl, and that about 40 million adults have levels exceeding 240 mg/dl. The age adjusted prevalence of Americans aged 20 years and older with LDL cholesterol of more than I 30 mg/dl is about 48% for men and 43% for women, and it is 18% for men and 5% for women with HDL cholesterol of less than 35 mg/dl6. Other components of lipoprotein particles thought to play a role in the atherosclerotic process include lipoprotein-a [Lp(a)] and

the ratio between apolipoprotein AI (apo A-1) and apolipoprotein B (apo B).

Plasma cholesterol and stroke

The level of plasma cholesterol has not been consistently shown to be a predictor of stroke risk. Observational cohort studies have failed to demonstrate an association between cholesterol levels and stroke incidence. A large prospective observational study of middle-aged men found no relationship between plasma total cholesterol concentration and 16.8 years incidence of fatal or non-fatal stroke. However, in contrast, the MRFIT study in 350,977 men aged 35-57 years found that a clear relationship emerged when stroke was categorised into ischaemic (thrombotic and embolic) and haemorrhagic types, the risk of ischaemic stroke increasing with total cholesterol concentration. Conversely, the risk of haemorrhagic stroke was highest at the lowest total cholesterol concentrations.

Multiple logistic regressions, adjusting for non-lipid risk factors for stroke, confirmed the independent association of low HDL-c and HDL-c/Apo Al with all strokes as well as with subtypes. Raised plasma oxidised LDL (OxL DL) has been found to be significantly associated with acute ischaemic stoke

Hdl cholesterol and stroke

As a risk factor in atherosclerosis, low HDL-c concentrations might be expected to contribute to stroke risk.

This is supported by a number of small case control studies and a large prospective study' over 16.8 years, which found that higher levels of HDL-c were associated with a significant decrease in risk of non-fatal stroke. The significant role of HDL in stroke as a risk factor has been echoed in other studies too.

In a recent study it has been shown that in contrast to high LDL-c level, low HDL-c level is a risk factor for mortality from CHD and stroke in old age. Further ultrasonographic intima-media thickness (IMT) studies in carotid arteries show that HDL-c concentration is inversely associated with atheroma burden.

Triglycerides and stroke

Plasma triglyceride concentrations have not appeared as significant independent risk factor in the studies cited above, but these studies examined other lipids as risk factors. A follow-up cohort study of screeners for the BIP trial reported triglyceride concentrations to be positively and independently predictive of stroke, but likely selection bias limits ability to generalised this to populations.

Lipoproteins as potential stroke risk factors

It has been observed that lipoprotein (a) levels are twice as high in patients with large vessel disease as opposed to patients with small vessel pathology. However studies have failed to establish a clear connection between individual apolipoproteins (Apo) and stroke risk. There are contradictory reports regarding lipoprotein(a) as a predictor of ischaemic stroke The association of ApoE, and its specific alleles with cerebrovascular disease is also controversial". In few studies in which they have been measured, Apo B and Apo A I seem to associate predictable as risk factors with LDL-c and HDL-c respectively.

Acute and long-term changes in serum lipids after acute stroke

It has been observed that the level of blood lipids fluctuates after stroke. Stroke is accompanied by transient reduction in blood lipid and lipoprotein levels. In a study serum cholesterol was found to fall progressively after acute stroke, but by 3 months

returned to levels comparable to those 48 hours after the stroke.

Similar results were observed by Mendez et al., who reported a significant fall in LDL levels on the 7th day of stroke and significantly higher levels after 3 months. The mechanism of lipid changes remains unclear, but it is thought to relate in part to the stress and the associated catecholamine overproduction in acute stroke. Poor nutrition and newly developed liver and renal dysfunction are also probable causes of these changes. Ideal time for the measurement of serum lipids after stroke is debatable, however, the lipid levels measurement at the time of admission may be a better representative of the lipid levels, because poor nutrition and newly developed liver and renal dysfunction after stroke may result in lower cholesterol level 3 months later, in addition the measurement at admission will include both fatal as well as non-fatal strokes.

Effect of lipid - lowering therapies on stroke prevention

To date, no large randomized trial with stroke as the primary end point has been completed to establish whether cholesterol reduction reduces stroke incidence. Indeed primary end points in clinical trials using lipid-lowering therapies (LLTs) were usually coronary events and/or mortality.

Overviews of these randomized trials have suggested that cholesterol lowering could be effective in reduction of stroke incidence. Particularly, only the newest class of cholesterol-lowering drug, the hydroxymethyl glutaryl coenzyme. A reductase inhibitor (Statins), were efficient in stroke reduction in this meta-analysis.

Fibrate Trials

Meta-analysis of the three trials using clofibrate showed that treatment actually increased the risk of all stroke, but did not influence non-fatal stroke. Of the six trials in aggregate, only one showed benefit, two showed no effect and three (all clofibrate) showed treatment to be detrimental.

Statins

The introduction of statins into clinical practice as effective drugs to lower LDL-c levels, has revolutionized coronary disease prevention, particularly in secondary care. Studies using simvastatin, pravastatin, lovastatin and atorvastatin have shown relative risk reduction in CHD events to the order of 20-35%. A meta-analysis of the effect of statin therapy including CARE specifically on stroke risk, concluded that treatment with statins led to an overall risk reduction of 31%.

Studies such as MIRACL, HPS and ASCOT have confirmed the efficacy status of statins in stroke prevention. In a recent meta-analysis5, which included all randomized clinical trials testing LLT, (statins and non- statins) there was strong evidence in favour of LLTs to prevent stroke. It showed that LLTs significantly reduced all stroke incidence (fatal plus non-fatal strokes) by I 7%. Statins individually reduced stroke incidence by 26% ($p<0.001$).

In the meta-analysis it was estimated that statins are more effective in patients in whom the incidence of stroke recurrence is much higher (~8%), and in them statins in such population could prevent stroke for 1000 patients treated during I year. This is close to the benefit obtained with antithrombotic drugs in secondary prevention of stroke. If such result is confirmed in further studies, this could place statins in the first line of treatment in stroke prevention.

Why only statins and not other LLT drugs (fibrates) or diet, are successful in stroke prevention remains

unresolved. Statins in addition to their lipid-lowering effects, have been demonstrated to have a wide variety of effects, such as anti-inflammatory, antithrombotic, neuroprotective, and direct properties on endothelial cells and plaque stability, which may act on stroke prevention.

Dietary fat and risk of stroke

Studies point out that monounsaturated and polyunsaturated fats seem to be beneficial, but saturated fats and trans unsaturated fatty acids increase risk of CHD. However, these associations do not seem to apply to stroke. Studies have suggested an inverse relation between saturated fat or trans unsaturated fat intake and risk of stroke. Although epidemiological studies indicate beneficial effect of some specific fatty acids such as long chains omega 3 polyunsaturated fatty acid, linolenic acid and linolenic acid on ischaemic stroke, few studies have directly related intake of dietary fat to risks of subtypes of stroke, and the results have been inconsistent

Conclusion

Haemorrhagic and ischaemic strokes share two common features, they arise out of defects in arteries and they damage the brain. In most other respect they differ. This probably accounts for the confusion about the role of dyslipidaemia as a risk factor when these two main stroke types are not distinguished. When studies make the distinction, the balance of observational evidence suggests that dyslipidaemia, particularly high LDL-c and low HDL-c, is an important risk factor for thromboembolic stroke. Low HDL-c and raised plasma oxidised LDL (Ox LDL) levels are significantly associated with risk of ischaemic strokes. Low HDL-c has been associated with increased risk of haemorrhagic strokes. Statins have shown to significantly lower the risk of stroke, though no large randomized trial with stroke as the primary end point is there to substantiate it. Evidence-base for other cholesterol-lowering treatments is less convincing. Patients with lipid abnormalities must be given the benefit of treatment as early as possible.

References

1. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet. 1997; 349:1269-1276.

2. Wolf PA, D Agostino RB. Epidemiology of stroke. In Barnett HJM, Mohr JR Stein BM, et al. eds. Stroke: Pathophysiology, Diagnosis and Management. New York, NY: Churchill Livingstone; 1998; 3-28.

3. Goldstein LB, Adams R, Becker, et al. Primary prevention of ischaemic stroke: a statement for health professionals from the stroke council of the American Heart Association. Stroke. 2001; 32:280-299.

4. Papadakis JA, Mikhailidis DP Winder AF. Lipids and stroke: neglect of a useful preventive measure? Cardio as. Res. 1988; 40:265-71.

5. Corvo lJC, Bouzamondo A, Sirol M, HulotJS, Sanchez R Lechat. R Differential effects of lipid-lowering therapies on stroke prevention: A meta-analysis of randomized trials. Arch Int. Med. 2003; 163(6): 669-676.

6. American Heart Association; 2001 Heart and Stroke Statistical Update. Accessible at http:// www. American heart. org/ statistics.

7. Sacco RL: Newer risk factors for stroke. Neurology 2001, 57(Suppl 2): S3 1-34.

8. Amarenco R Hyper cholesterolemia, lipid-lowering agents, and the risk for brain infarction. Neurology 2001; 57 (Suppl. 2): S35-S44.

9. Wannamethee SG, Shaper AG, Ebrahim S. HDL cholesterol, total cholesterol, and the risk of stroke in middle-aged British men. Stroke. 2000; 311:882-8.

10. Shahar E, Chambless LE, Rosamond WD et al. Plasma lipid profile and incident ischemic stroke: The atherosclerosis risk in communities (ARIC) study. Stroke. 2003; 34:623-3 I.

11. Prospective studies collaboration. Cholesterol, diastolic blood pressure and stroke: I 3,000 strokes in 450,000 people in 45 prospective cohorts. Lancet 1995; 346: 1647-53.

12. Atkins D, Psaty BM, Koepsell TD, Long streth WT, Jr., Lassen EB. Cholesterol reduction and the risk for stroke in men. A meta-analysis of randomized, controlled trials. Ann. Inter Med. 1993; I 19: 136-45.

13. Iso H, Jacobs DR, Jr., Wentworth D, Neat on JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. N. Engl. J. M ed. 1989; 320: 904-10.

14. Horenstein RB, Smith DE, Mosca L. Cholesterol predicts stroke mortality in the Women's Pooling Project. Stroke 2002; 33: 1863-8.

15. Denti L, Cecchetti A, Annoni Y Merli MF, Ablondi F, Valenti G. The role of lipid profile in determining the risk of ischaemic stroke in elderly: a case-control study. Arch Gerontol, Geriatr., 2003; 37: 51 -62.

16. Hachinski V, Graffagnino C, Beaudry M, et al. Lipids and stroke a paradox resolved. Arch Neurol. 1996; 53: 303-308.

17. Sridharan R. Risk factor for ischemic stroke: a case control analysis. Neuroepidemiology 1992; I 1:24-30.

18. Bots ML, Elwood PC, Nikitin Y et al. Total and HDL cholesterol and risk of stroke. EUROSTROKE: a collaborative study among research centres in Europe. J. Epidemiol Community Health. 2002; 56 (Suppl I): 119-24.

19. Sacco RL, Benson RT, Kargman DE, et al. High-density lipoprotein cholesterol and ischaemic stroke in the elderly: the Northern Manhattan Stroke Study. JAMA 2001,285: 2729-2735.

20. Morag NK, Tanne D, Graft E, Gold bourt U. Low- and high-density lipoprotein cholesterol and ischaemic cerebrovascular disease. Arch Intern. Med. 2002; 162: 993-999.

21. Mannami T, Konishi M, Baba S, Nishi N, Terao A. Prevalence of asymptomatic carotid atherosclerotic lesions detected by high-resolution ultrasonography and its relation to cardiovascular risk factor in the general population of a Japanese city: the Suita study. Stroke 1997; 28:518-25.

22. Tanne D, Morag NK, Graff E, Gold bourt U. Blood lipids and first-ever ischemic stroke/transient ischaemic attack in bezafibrate infarction prevention (BIP) registry. High triglycerides constitute an independent risk factor. Circulation 2001; 104: 2892-2897.

23. Cerrato R Imperiale D, Fornengo R et al. Higher lipoprotein(a) levels in atherothrombotic than lacunar ischaemic cerebrovascular disease. Neurology. 2002; 58: 653-655.

24. Macleod MJ, DeLaugl RR Breen G, Meikljohn D, Lemmon H, Clair DS. Lack of association between apolipoprotein E genotype and ischaemic stroke in a Scottish population. Eur. J. Clin. Invest. 2001; 30: 570-3.

25. Djousse L, Myers RH, Province MA et al. Influence of apolipoprotein E, smoking and alcohol intake on carotid atherosclerosis: National heart, lung, and blood institute family heart study. Stroke. 2002; 33:1357-61.

26. Meudez I, Hachinski V, Wolfe B. Serum lipid after stroke. Neurology. 1987; 37:507-51 I.

27. Hollanders FE, Shafar J. Serum lipid following completed stroke syndrome. Postgraduate Medical Journal. 1975; 51:386-389.

28. Woo J, Lam CWK, Kay R, Wong HY, Teoh R, Nicholls MG. Acute and long-term changes in serum lipids after stroke. Stroke 1990; 21; 1407-1 I.

29. Blauw GJ, Lagaay AM, Smett AH, Westendnep RG. Stoke, statin and cholesterol: A meta-analysis of randomized, placebo controlled, double-blind trials with HMG-Co A reductase inhibitors. Stroke. 1997; 28: 946-950.