

STATINS ARE PROTECTIVE AGAINST DEMENTIA

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Vascular changes are evident in the brains of patients with different types of dementias. Even in the first neuropathological investigation of Auguste D.'s brain, Alois Alzheimer described vascular changes besides neuritic plaques and neurofibrillary tangles (1). The importance of vascular changes in the development of dementia is well established after the NUN study. Plaques and tangles are necessary but sometimes they are not sufficient to cause a dementing illness (2). Vascular changes are not limited to atherosclerosis; blood brain barrier changes, cerebral amyloid angiopathy, and micro bleeds may also cause dementia. These vascular changes usually develop as a result of long time exposure to the vascular risk factors. Strokes, atherosclerosis, hypertension, diabetes mellitus, heart disease, dyslipidemia are thought to be causes for neurodegeneration, vascular dementia and Alzheimer's disease (3).

Several longitudinal population studies revealed that the existence of the midlife vascular risk factors usually resulted in a cognitive impairment, sometimes dementia (4, 5).

Statins are cholesterol lowering drugs that inhibit hydroxyl methyl glutaryl coenzyme A and cause a reduction in blood cholesterol levels, especially in LDL-C levels. They also show a pleiotropic effect via isoprenoid reduction; regulate nitric oxide metabolism, have anti-inflammatory effect (inhibit the production of adhesion molecules and proinflammatory cytokines), inhibit angiogenesis in some chronic disease (ie. macular degeneration and some cancers) but promote angiogenesis in cardiovascular disease. They also have anti platelet and antithrombotic action. Recently; with the better understanding of amyloid beta metabolism in the brain; the role of cholesterol has become evident in the amyloidogenic pathway of the beta amyloid precursor protein cleavage (6).

Evidence for the effectiveness of statins in dementia protection, mostly comes from observational studies. In a recent meta-analysis, Wong et al. reported a slight benefit for the prevention of AD and all types of dementia with statin use. A subgroup analysis of ginkgo evaluation of memory study showed protective effects of statins in healthy individuals, but not in patients with mild cognitive impairment and dementia. Lipophilic statins tended to reduce dementia risk more than the hydrophilic ones (7, 8, 9).

Numerous studies using statins for prevention or treatment of dementia revealed negative results (10, 11, 12,13, 14).

The factors underlying the failure of transferring the success of epidemiological studies to the prevention studies may be as follows:

Nearly all patients recruited for the studies were in late old age (15).

Patients enrolled to the studies were mostly cognitively impaired in some degree.

Most of the studies excluded hypercholesterolemic patients which were the main target of the statin treatment.

We all are aware of the fact that, Alzheimer's disease's and most of the other dementias' pathologic process begins long before the disease becomes evident. Statin treatment must be initialized in midlife (for the patients with hypercholesterolemia) and continued for a prolonged follow up period to achieve a possible success.

And finally we have to find a way to follow the effect of statins on the disease process such as structural and functional biomarkers (16, 17).

References:

- 1) Förstl H and Levy R. Über eigenartige Krankheitsfälle des späteren Alters: (On certain peculiar diseases of old age) *History of Psychiatry* March 1991; 2: 74-101.
- 2) Mortimer JA. The Nun Study: Risk Factors for Pathology and Clinical-Pathologic Correlations. *Curr Alzheimer Res* 2010; 9: 621-627.
- 3) Kalaria RN. Vascular Basis for Brain Degeneration: Faltering Controls and Risk Factors for Dementia. *Nutr Rev.* 2010; December; 68(Suppl 2): S74-s87.

- 4) Strand BH, Langballe EM, Hjellvik V et al. Midlife vascular risk factors and their association with dementia deaths: Results from a Norwegian prospective study followed up for 35 years. *J Neurol Sci.* 2013 Jan 15; 324(1-2):124-130.
- 5) Kivipelto M, Helkala EL, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ.* 2001; 322(7300):1447-1451.
- 6) Miida T, Takahashi A, Ikeuchi T. Prevention of stroke and dementia by statin therapy: experimental and clinical evidence of their pleiotropic effects. *Pharmacol Ther.* 2007 Feb;113(2):378-93.
- 7) Wong WB, Lin VW, Boudreau D, Devine EB. Statins in the prevention of dementia and Alzheimer's disease: A meta-analysis of observational studies and an assessment of confounding. *Pharmacoepidemiol Drug Saf.* 2012 Dec 6. doi: 10.1002/pds.3381. [Epub ahead of print].
- 8) Bettermann K, Arnold AM, Williamson J et al. Statins, risk of dementia, and cognitive function: secondary analysis of the ginkgo evaluation of memory study. *J Stroke Cerebrovasc Dis.* 2012 Aug;21(6):436-44.
- 9) Shepardson NE, Shankar GM, Selkoe DJ. Cholesterol level and statin use in Alzheimer disease: I. Review of epidemiological and preclinical studies. *Arch Neurol.* 2011;68(10):1239-1244.
- 10) Trompet S, van Vliet P, de Craen AJ et al. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. *J Neurol.* 2010 Jan;257(1):85-90.
- 11) Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomized placebo-controlled trial. *The Lancet* 2002;360:7-22.
- 12) Shepardson NE, Shankar GM, Selkoe DJ. Cholesterol level and statin use in Alzheimer disease: II. review of human trials and recommendations. *Arch Neurol.* 2011;68(11):1385-1392.
- 13) Sano A, Bell KL Galasko D, et al. A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. *Neurology.* 2011;77(6):556-563.
- 14) Feldman HH, Doody RS, Kivipelto M, et al. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. *Neurology.* 2010;74(12):956-964.
- 15) Li G, Shofer JB, Rhew IC et al. Age-varying association between statin use and incident Alzheimer's disease. *J Am Geriatr Soc.* 2010 Jul;58(7):1311-7.
- 16) Burgos JS, Benavides J, Douillet P et al. How statins could be evaluated successfully in clinical trials for Alzheimer's disease? *Am J Alzheimers Dis Other Demen.* 2012 May;27(3):151-3.
- 17) Wolozin B. Statins and therapy of Alzheimer's disease: questions of efficacy versus trial design. *Alzheimers Res Ther.* 2012;4(1):3.