

STATINS AND CATARACT - CONTROVERSIES

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Abstract: Statins are one of the major therapeutic classes, being responsible for many pleiotropic cardiovascular effects, anti-inflammatory action, immune support and prevention of osteoporosis. Lens penetration by statins involves a series of local changes with inherent repercussions on eye morphology. The link between statins and the initiation of cataract process was the subject of many studies, their results still maintaining controversy over this link.

Cuvinte cheie: statine, cataracta, controversie

Rezumat: Statinele reprezintă una dintre cele mai importante clase terapeutice, caracteristicile pleiotrope fiind responsabile de numeroase efecte cardiovasculare, antiinflamatorii, de susținere a sistemului imunitar și prevenire a osteoporozei. Penetrarea cristalinului de către statine implică o serie de modificări locale cu repercusiuni inerente asupra morfologiei oculare. Legătura dintre statine și apariția cataractei a reprezentat obiectul a numeroase studii, rezultatele lor menținând în continuare controverse asupra acestei legături.

More than 100 ago, Virchow noted the presence of cholesterol into the blood vessels wall of people who died as a result of obstructive vascular diseases such as myocardial infarction. With the publication of the Framingham study results, the one who held definite correlation between hypercholesterolemia and coronary heart disease, research has started on the synthesis of lipid-lowering agents, especially those able to stop endogenous cholesterol synthesis. The key enzyme involved in this process is 3-hydroxy-3-glutaryl-coenzyme A reductase (HMGCR) and the target for therapeutic class being represented by statins.(1,2)

The justification for the widespread use of statins to reduce cardiovascular morbidity and mortality has been brought by the 4S, Scandinavian Simvastatin Survival Study.(3) Subsequently, numerous studies have supported, beyond any doubt, the major impact of statins on cardiovascular protection.(4) Moreover, it was shown that the mechanisms by which this class of medications significantly reduce cardiovascular risk is not represented only by the decreasing of cholesterol levels, but also by a series of biochemical changes known as pleiotropic effects.(5) Statin intervention is a pluripotent one, targeting endothelial dysfunction, antiplatelet effects, antioxidant, anti-inflammatory (6), neuroprotective, immune support and prevention of osteoporosis (7). In addition, it was demonstrated that statins penetrate the lens.(8) With advancing age, the risk of degenerative changes crystal under the influence of oxidative stress increases. There is ample evidence attesting an inverse association between dietary intake of antioxidants and senile cataract.(9,10,11). However, both risk factors and protective ones seem to be different depending on the type of cataract. The nuclear cataract is associated with smoking, the cortical cataract is subsequent to exposure to ultraviolet radiations and posterior subcapsular cataract occurs in connection with hypertension and use of steroid preparations. Statins appear to confer protection against nuclear cataract, but with no favorable effect on cortical or posterior subcapsular cataract.(12) The explanation lies in the intimate biological

mechanisms which contribute to the building of nuclear cataract, namely oxidative stress and inflammation, processes thwarted by statins.(6) In addition, it was shown experimentally in dogs that, although the initial focus of statins is especially in the cortex, the drug concentration is higher in the nucleus after a long period of administration.(8)

One of the most relevant studies that attest the favorable effects of statins in preventing the development and progression of nuclear cataract was published in 2006 in JAMA.(8) The authors followed 1299 subjects who were examined by scaled photographs of both eyes, patients considered to have a risk of nuclear cataract in the next five years, some of them (214 subjects) were being treated with statins, whom continued until the end of the study. In total, 210 people developed this type of cataract in the monitored period, the incidence was of 12.2% in the patients treated with statins compared with 17.2% in those who did not use this medication

Other studies (13,14,15) have not reported a protective effect of statins against nuclear cataract. There should be noted some objectionable aspects of these investigations. The degree of appreciation of nuclear sclerosis was not an objective one, based on shooting both eyes but on clinical examination, being difficult to be standardized between evaluators, the subjective impression of each being a possible generating errors element. Moreover, it is unclear if the evaluation was impartial in terms of treatment. It must not be overlooked that, upon approval by the FDA (Food and Drug Administration) in 1987 of the first statin (lovastatin), attention is drawn upon the ophthalmologic examination prior to initiating therapy and then annually starting from experimental data that showed the development of cataracts in dogs. Later, in 1991, this recommendation was withdrawn from lovastatin information package.

One study (18) published in 2001 revealed no increase in the incidence of cataracts in patients treated with statins. However, the authors could not exclude ocular adverse effects at higher doses than 20 mg (the dose used in these patients). Based on this observation, the authors have taken into account the

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circumstances that determine exposure to high serum levels of statins such as the concomitant use of drugs that are metabolized by the same pathway as statins (except pravastatin), namely cytochrome P450.(19) Studies have shown that such a combination lead to increased systemic availability of statins, which involve a higher risk of side effects such as myopathy and rhabdomyolysis.(20,21) Medications that increase 5-10 times systemic levels of statins include erythromycin, verapamil (22), ketoconazole (23) and cyclosporine.(21) The authors concluded that co-administration of erythromycin and statins would increase the risk of developing cataracts by 2-3 times. Two years later, another important study (24) conducted on two groups of 15 000 patients each, demonstrated that the use of statins on short and medium term (up to 4.5 years) is associated with an increased risk of cataract development. However, it should be noted that statin therapy is a long one for most patients, so further studies are needed to assess the impact of these drugs on lens in long-term administration.

A study was published last year (25), including a significant number of patients (6972), which concluded that patients who used statins had a higher risk of developing cataracts compared with controls. Based on these results, the authors emphasize the importance of a sensible approach to statin therapy, especially in primary cardiovascular prevention; additional studies are needed in that direction. Despite the large number of patients included, some deficiencies of this study were revealed: retrospective design, lack of data on cataract visual significance, using pharmaceutical data on the use of statins. The results of a meta-analysis (26) were presented last year at the European Congress of Cardiology. This meta-analysis included 2399200 people, of whom 25618 were detected with cataract. The mean duration of statin therapy was 54 months and the average patient age was 61 years old. Prof. Kostis' conclusions were clear: statins decrease the incidence of cataract by 20% and the risk was reduced with 50% when treatment was initiated early (in the decade 40-49 years old) and with a longer duration (up to 14 years). Conflicting results of different studies highlight that additional assessments are needed to clarify these controversies. Investigations suggesting the favorable effect of statins in delaying nuclear cataracts could be the basis for new studies focused on evaluating the lens in patients already enrolled in clinical trials that are in progress or in the planning stage. Implications for the health system could be particularly important as nuclear cataract is the most common type of age-related cataracts.

REFERENCES

- Chicea L. Statinele – farmacologie, profil de siguranță, reacții adverse, indicații, contraindicații, posologie, in Medicamente cu efect adjuvant in tratamentul hepatopatiilor cronice si al hemopatiilor maligne, sub redactia R.Mihaila, Ed. ULBS; 2008. p. 46-59.
- Frier M, Truswell AS, Shephard J, A de Looy, Jung R. Diabetes Mellitus, nutritional and metabolic disorders, in Davidson's principles and practice of Medicine, Seventeenth edition, Churchill Livingstone, p.537.
- Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S), Lancet 1994 Nov 19;344(8934):1383-9.
- McPhee SJ, Papadakis M. Lawrence M Tierney Jr, Current Diagnosis and Treatment; 2008. p. 456-478.
- James K.Liao and Ulrich Laufs, Pleiotropic effects of statins, www.ncbi.nlm.nih.gov/pubmed/15822172.
- Albert MA, Danielson E, Rifai N, Ridker PM, Effect of statin therapy on C-reactive protein levels; the Pravastatin Inflammation/CRP Evaluation (PRINCE): a randomized trial and cohort study JAMA 2001;286:64-70.
- Saunders WB. Diseases of bone and mineral metabolism – osteoporosis, in Cecil, Textbook of Medicine, 22th Edition 2004; p. 566-580.
- Ekklein B, Klein R, Lee KE, Grady LM. Statin Use and Incident Nuclear Cataract JAMA 2006, 295: 2752-2758.
- Vitale S, West S, Hallfrisch L et al. Plasma antioxidants and the risk of cortical and nuclear cataract. Epidemiology 1993;4:195-203.
- Jacquest PF, Chylack LT Jr, McGaudy RB, Hartz Sc, Antioxidant status in person with and without senile cataract. Arch Ophthalmol 1998;106:337-340.
- Leske MC, Chylack LT Jr, Wu SY, The Lens Opacities Case-Control study: risk factors for cataract. Arch Ophthalmol 1991;109:244-251.
- McCarthy CA, Murkesh BN, Guymer RH, Baird PN, Cholesterol-lowering medications reduce the risk of age-related maculopathy progression, Med J Aust 2011;175-180.
- Sweet L, Hubbard R, Fletcher AE, Cataract and the use of statins: a case-control study, QJM 2003;96:337-343.
- Haris ML, Bron AJ, Brown NA et al, Absence of effect of simvastatin on the progression of lens opacities in a randomised placebo controlled study: Oxford Cholesterol Study Group. BR J Ophthalmol 1995;79:996-1002.
- Schmidt J, Schmidt C, Hockwin O. No lens changes caused by simvastatin results from a prospective drug safety study, Lens Eye Toxic Res 1990;7:643-650.
- Gerson RJ, MacDonald JS, Alberts AW et al. On the etiology of subcapsular lenticular opacities produced in dogs receiving HMG-CoA reductase inhibitors. Exp Eye Res 1990;5065-78.
- Hartman HA, Myers LA, Evans M, Robinson RL, Engstrom RG. The safety evaluation of fluvastatin, an HMG-CoA reductase inhibitor, in beagle dogs and rhesus monkeys. Fundam Appl Toxicol 1996;2948-62.
- Raymond G. Schlienger, Walter E. Haefeli, Hershel Jick, Christoph R. Meier, Risk of Cataract in Patients Treated With Statins, Arch Intern Med 2001;161(16):2021-2026.
- Desager JP, Horsmans Y. Clinical pharmacokinetics of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. Clin Pharmacokinet 1996;31348-371.
- Bottoff M, Hansten P. Long-term safety of hepatic hydroxymethyl glutaryl coenzyme A reductase inhibitors. Arch Intern Med 2000;1602273-2280.
- Gruer PJ, Vega JM, Mercuri MF, Dobrinska MR, Tobert JA. Concomitant use of cytochrome P450 3A4 inhibitors and simvastatin. Am J Cardiol 1999;84811-815.
- Kantola T, Kivistö KT, Neuvonen PJ. Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. Clin Pharmacol Ther 1998;64177-182.
- Gilad R, Lampl Y. Rhabdomyolysis induced by simvastatin and ketoconazole treatment. Clin Neuropharmacol 1999;22295-297.
- Smeeth L, Hubbard R, Fletcher AE. Cataract and the use of statins: a case - control study. QJM 2003;9695):337-343.
- Leuschen J, Mortensen EM, Frei CR, Mansi CM, Panday V, Mansi I. Association of Statin Use With Cataracts: A Propensity Score-Matched Analysis, JAMA Ophthalmol. 2013;131(11):1427-1434.
- Kostis J, Dobrzynski L. Prevention of Cataracts by Statins: A Meta-Analysis, J Cardiovasc Pharmacol Ther 1074248413511690, first published on December 4, 2013.