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COMMENTARY

Association of blood lipid levels with the risk of intracranial aneurysm formation and rupture calls for further studies: A commentary on the article by Zhang et al.

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Blood levels of cholesterol in circulating low-density lipoprotein (LDL) and high-density lipoprotein (HDL) vesicles are an established causative risk factor for atherosclerotic and other cardiovascular diseases. Moreover, LDL and HDL levels are the target of a multitude of pharmaceutical and nonpharmaceutical therapies (e.g., exercise and diets) that reduce the risk for cardiovascular end events.

Although LDL and HDL have been shown to accumulate in the wall of human intracranial aneurysms (IAs), where they associate with degeneration and inflammation of the wall [1, 2], the role that circulating lipid levels play in the pathogenesis of IA formation and rupture remains unclear. Even more controversial is the potential use of statins or other lipid-lowering drugs to reduce the formation or growth (i.e., risk of rupture) of IAs, because clinical case–control studies report contradictory results [3, 4], although some statins have shown promising results in controlled animal models [5, 6]. Statins have, however, many other biological effects on the remodeling artery wall other than lowering circulating LDL [7], which may very well explain at least part of this apparent contradiction.

Zhang et al. [8] shed new light on the topic with a new approach. They use Mendelian randomization, a method of genetic epidemiology, to study the role of LDL and HDL levels in the formation and rupture of IAs. This approach has the advantage of avoiding the concomitant pleiotropic effects that a medication may have, as well as humans having variable levels of commitment to the use of any medication that they claim to use. Moreover, it has the advantage of studying the association of a lifelong exposure, instead of comparing measurements from a single point of time with the clinical course of a disease that develops over time, or in the case of some aneurysms, over decades.

The observation by Zhang et al. that genetic polymorphism predisposing to high HDL is associated with a lower risk of formation and rupture of IAs could imply that lifestyle changes raising HDL levels might reduce the risk of aneurysmal subarachnoid hemorrhage. Similarly, the observation that high LDL levels are associated with lower risk of IA formation is of great interest. That the genetic proxies for 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors were associated with increased risk of IA formation and rupture is also something to think about, although caution is warranted when extrapolating this observation to clinical practice. What we can, however, safely conclude from the data reported by Zhang et al. is that levels of circulating cholesterol particles seem to affect the risk of IA formation and rupture. This in turn encourages new studies on the potential diagnostic use of circulating lipid levels or markers associated with them, to identify rupture-prone aneurysms. Moreover, it encourages studies on the effects that diet, exercise, and other lipid level-modifying lifestyle changes may have on the risk of IA formation and aneurysmal subarachnoid hemorrhage. It may well turn out that adopting healthy living habits, in addition to cessation of smoking, reduces the risk of aneurysmal rupture more than thus far thought.

AUTHOR CONTRIBUTIONS

Juhana Frösen: Conceptualization (equal); writing – original draft (equal).

See paper by B. Zhang et al. on page 2967.

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CONFLICT OF INTEREST

The author has no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

1. Frösen J, Tulamo R, Heikura T, et al. Lipid accumulation, lipid oxidation, and low plasma levels of acquired antibodies against oxidized lipids associate with degeneration and rupture of the intracranial aneurysm wall. *Acta Neuropathol Commun*. 2013;1:71.
2. Ollikainen E, Tulamo R, Lehti S, et al. Smooth muscle cell foam cell formation, apolipoproteins, and ABCA1 in intracranial aneurysms: implications for lipid accumulation as a promoter of Aneurysm Wall rupture. *J Neuropathol Exp Neurol*. 2016;75:689-699.
3. Marbacher S, Schläppi JA, Fung C, Hüsler J, Beck J, Raabe A. Do statins reduce the risk of aneurysm development? A Case-Control Study. *J Neurosurg*. 2012;116:638-642.
4. Yoshimura Y, Murakami Y, Saitoh M, et al. SSS research group. Statin use and risk of cerebral aneurysm rupture: a hospital-based case-control study in Japan. *J Stroke Cerebrovasc Dis*. 2014;23:343-348.
5. Aoki T, Kataoka H, Ishibashi R, Nozaki K, Hashimoto N. Simvastatin suppresses the progression of experimentally induced cerebral aneurysms in rats. *Stroke*. 2008;39:1276-1285.
6. Aoki T, Kataoka H, Ishibashi R, et al. Pitavastatin suppresses formation and progression of cerebral aneurysms through inhibition of the nuclear factor kappaB pathway. *Neurosurgery*. 2009;64:357-365.
7. Zhou Q, Liao JK. Pleiotropic effects of statins. - basic research and clinical perspectives. *Circ J*. 2010;74:818-826.
8. Zhang B, Dong S, Miao Y, et al. Effects of blood lipids and lipid-modifying drugs on intracranial aneurysms. *Eur J Neurol*. 2022;29:2967-2975.