Paradigm Shift in Lipid Nutrition for the Prevention of Ischemic Stroke

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EDITORIAL

Ischemic stroke and coronary heart disease (CHD) share common mechanisms through blood circulation, but their relationships with cholesterol levels are different. In the case of CHD, "the lower, the better" hypothesis with regards to cholesterol has prevailed so far in clinical fields, setting upper limits of cholesterol levels and advising maintenance of the levels below the limits. However, the mortality ratio of the highest to lowest cholesterol levels (relative risk, RR) varies much among selected populations. We interpreted that the RR value is a surrogate marker of the proportion of familial hypercholesterolemia (FH) cases in the population or subpopulation selected [1]. As the CHD mortality of the FH cases is >10 times greater than that of the non-FH cases, and the survival of FH cases is generally shorter, the proportion of FH is expected to decrease along with ageing, and so does the RR value [1]. Because of genetically impaired LDL receptor functions, the FH cases develop hypercholesterolemia from young ages. However, high plasma cholesterol levels per se are unlikely to be the major causative factor for CHD, because 1 a high cholesterol level does not necessarily lead to CHD among general populations over 40-50 years of age, when atherogenesis is rapidly in progress, 2 in the FH cases, no significant difference is observed in average cholesterol levels between those who died of CHD and those still alive, 3 in FH patients, tissue damage precedes plaque formation in the artery [2], and 4 statins lower LDL-C levels significantly but they are ineffective in preventing CHD. In the FH cases, a persistently restricted supply of energy (triacylglycerol) carried by LDL would damage coronary artery cells leading to CHD just as in non-FH cases with thrombosis at the coronary artery.

One might argue that statins are effective in decreasing both LDL-C levels and CHD mortality rate. Indeed, many clinical studies reported in 1990s that they were effective in preventing CHD events by approximately 30%. However, ethical problems were exposed in clinical studies performed mainly by industrial scientists. In the EU, new penal regulations on clinical trials came into effect in 2004 [3]. All the clinical trials performed after 2004 by scientists free of “conflicts of interest” reported that various statins lowered LDL-C levels, but they were ineffective in preventing CHD, again supporting the interpretation that high LDL-C levels per se are not a causative factor for CHD [1,4].

Some follow-up studies on general populations revealed that a small number of people with extremely high cholesterol levels exhibit a significantly high CHD mortality, and we interpreted that this reflects FH cases confined to the highest cholesterol group [4]. In the case of ischemic stroke, mortality and cholesterol levels are inversely associated, and the possible impact of FH cases was not apparent in the follow-up studies; no elevation of stroke mortality was observed even in the highest cholesterol group. Interpret that this difference is due to the fact that the heart depends on the LDL receptor for its energy supply whereas the brain does not; the brain synthesizes triacylglycerol and cholesterol within the organ, and is not affected much by impaired LDL receptors.

Despite the absence of positive associations between LDL-C and ischemic stroke, statins have been used frequently for the prevention of stroke, at least in the clinical fields in Japan. Some scientists continue to claim that statins are effective in reducing cerebrovascular events, on the basis of meta-analyses. However, we did not consider this conclusion from such meta-analyses of reports including those published before 2004 to be reliable, when we published the New Cholesterol Guidelines for Longevity 2010 [4].

Recently, biochemical mechanisms underlying statin actions have been well clarified, and the observed increase in the incidence of newly-onset diabetes mellitus by statin administration can be explained to be due to the following: 1 decreased cholesterol levels at the raft structure of plasma membranes where the insulin receptor is localized, 2 decreased levels of dolichol, which is synthesized from a prenyl intermediate of cholesterol biosynthesis and is essential for the proper glycosylation of the insulin receptor, 3 decreased levels of isopentenyl-adenine, which is essential for the synthesis of the Se-containing protein involved in signal transduction of the insulin receptor, 4 decreased levels of CoQ and heme B, which
are essential for the mitochondrial electron transport/oxidative phosphorylation system to synthesize adenosine triphosphate (ATP) and the ketone bodies, which are used as an energy source in diabetes mellitus, and 5 reduced prenylation of the Rho (small GTPase) protein, which is necessary for insulin release. Statins are mitochondrion-toxic and cytoxic as confirmed clinically using skeletal muscle samples [5].

In the brain/nervous system, cholesterol is utilized for myelin synthesis and is required for neurotransmission at synapses. Relevant adverse effects of statins include increased incidence of polyneuritis, cognitive disorder, decreased libido in both genders, and development of Parkinson’s disease (PD). PD is a progressive neurological condition resulting in movement problems such as stiffness, tremors and slurred speech. A recent study reported that continuous lipidophilic statin therapy was associated with increased incidence of PD as compared with discontinuation among statin users [6]. However, it is very likely that the doctors decided to take off the statins when the patients started to experience early symptoms, and then the patients developed full PD, and such patients were counted as those who stopped taking statins and got PD.

Similarly, a large-scale follow-up study performed in Finland reported that stroke mortality as well as all-cause, cancer, and CHD mortality was lower in the statin-user group than in the age and gender-matched non-user group [7]. The difference was prominent only within a couple of years after starting the statin therapy. Similar observations have been reported for heart failure patients. Needless to say, one cannot advise people to use statins on the basis of these observations, because 1 plasma cholesterol levels of the statin getUsers should have been higher than those of non-users, 2 cholesterol levels are inversely associated with mortality rates for these causes at >50 years of age [1,4], and 3 the observed lower mortality of the statin-user group likely reflects higher cholesterol levels and lower mortality rates. These points 1–3 also hold true for PD cases as lower LDL-C levels are associated with PD [8]. Therefore, it is critical to take into account the inverse association between cholesterol levels and mortality rates for these causes when statin users and non-users are compared.

Finally, I would like to emphasize that lipid nutrition based on the cholesterol hypothesis is wrong [1]. The evidence can be summarized as follows: 1 the cholesterol lowering effect of increasing the intake of linoleic acid-rich vegetable oils while decreasing those of saturated fats and cholesterol is transient, and no significant cholesterol lowering effect is observed after several years of such interventions. 2 long-term intervention based on the cholesterol hypothesis resulted in increased mortality rates for CHD [9], cancer, violent death and/or all causes [4], and 3 no positive association has been reported between CHD mortality and the intakes of saturated fatty acids and cholesterol, but rather inverse associations have been shown between dietary saturated fatty acids and/or cholesterol and mortality rate for ischemic stroke [10, and others].

In conclusion, high plasma LDL-C level is not a causative factor for atherosclerotic diseases but is a predictor of longevity for the majority of people, and the use of mitochondrion-toxic statins should be restricted to specific cases for which other medications are inappropriate.

**REFERENCES**