Rethinking Cholesterol Issues

Summary of the Cholesterol Panel Discussion at the 20th Annual Meeting of the Japan Society for Lipid Nutrition, 2011

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Introduction

The following panelists attended the meeting: Drs Yoichi Ogushi, Harumi Okuyama, Yasuo Kagawa, Rokuro Hama, Tomohito Hamazaki, and Akira Tanaka. In planning the panel, the chairpersons (YK and TH) invited experts from the Japan Atherosclerosis Society. Unfortunately, however, the Society declined to send any experts. Here, the abstracts of panelists’ presentations, both in favor of and against the cholesterol theory, and our comments (TH and HO) are provided. Issues regarding cholesterol have not been elucidated, especially in Japan. For example, all-cause mortality is actually lower in groups with high cholesterol levels compared with those with low levels according to most Japanese epidemiologic studies. The causal relationship between low cholesterol level and high all-cause mortality remains an important issue.

Does hypercholesterolemia induce coronary disease?
Akira Tanaka (Kagawa Nutrition University)
Since it was revealed in the Framingham Heart Study that the incidence of coronary heart disease (CHD) increases with blood cholesterol levels, especially above 220 mg/dL (Ann Intern Med 1971; 74: 1), the notion that hypercholesterolemia leads to the development of CHD has been confirmed by many clinical results worldwide. Also in Japan, the Particular Disease Research Group on Primary Hyperlipidemia of the Ministry of Health and Welfare reported in 1987 that high low-density lipoprotein (LDL)-cholesterol and low high-density lipoprotein (HDL)-cholesterol were associated with an increased incidence of CHD. Regarding the question of whether improvement of hypercholesterolemia is able to reduce the incidence of CHD, many intervention studies using statins have demonstrated since 1994 that the answer is “yes” (Lancet 1994; 344: 1383, N Engl J Med 1996; 335: 1001). It is generally accepted that increased LDL levels increase CHD and that treatment to reduce LDL levels prevents CHD.

The cholesterol controversy
Yasuo Kagawa (Kagawa Nutrition University)

1. All-cause mortality: Epidemiologic evaluation of cholesterol effects on CHD-related deaths does not provide significant results because of a lack of individuals in various categories, which has been shown clearly by Nago (J Epidemiol 2011; 21: 67).
2. Statin dosage: Studies with a low dose of statins have not generally shown significant results in terms of beneficial or adverse effects. Studies with a high dose have shown that statins are safe and effective in the short term (Curr Opin Lipidol 2005; 17: 625); however, we must wait for long-term results.
3. Molecular biology: We found that one of the causes of hyperlipidemia was a genetic polymorphism of fatty acid desaturase (Hum Genet 2010; 127: 685). Hypocholesterolemia is not associated with somatic cell mutation or immunity to cancer development. The surrogate marker of telomere counting for mortality supports the utility of statins (Lancet 2007; 369: 107).
4. Non-statin users: Statistics of the Japanese population are distorted by the use of statins. The reason that the average life-span of Mongolians, who do not use statins and eat a significant
amount of meat, is shorter than that of the Japanese by 17 years is not due to blood cholesterol levels but to low levels of folic acid and docosahexaenoic acid and high levels of oxidative stress (see Fig. 1, Curr Aging Sci 2009; 2: 214).

The significance of hypercholesterolemia treatment is notably low
Yoichi Ogushi (Tokai University)

Statins are widely used in women and in the elderly in Japan (Ministry of Health and Welfare of Japan 2008: Table 29-4). However, in the United States and Europe, it is considered that statin use is not necessary for women and the elderly. Ninety-five types of genetic mutation have been found by genetic analysis of familial hyperlipidemia, of which 81 (85%) are not related to cardiovascular disease risk (Nature 2010; 466: 707). Decreasing cholesterol levels with medication did not affect the development of intima–media thickness of coronary arteries in familial hypercholesterolemia (FH) (ENHANCE study, N Engl J Med 2008; 358: 1431). Statins are useful only for FH patients with symptoms such as xanthomas. The distribution of LDL-cholesterol levels in US patients with CHD admitted to hospital (Fig. 2, upper panel, Am Heart J 2009: 157: 111e2) was shifted to the left compared with the general Japanese
population. This fact explains why cholesterol lowering cannot prevent CHD. Cholesterol levels in blood show a strong correlation with albumin (Proceedings of IHEPA International Conference 2011: Session 3), and are suggested to be a good marker of longevity (especially in Japan). People with hyperlipidemia have a lower risk of developing stroke, suffer from milder symptoms if they do develop hyperlipidemia, and have a lower risk of death, even if admitted to hospital due to stroke (Japanese J Stroke 2010; 32: 242). The medical term “dyslipidemia” has therefore lost its *raison d’être*.

**Fig. 2.** LDL-C levels in US patients hospitalized due to CAD and in the Japanese general population. The upper panel (A) shows the distribution of LDL-cholesterol in US patients with coronary artery disease (CAD) on admission to hospital (Am Heart J 2009; 157: 111-117e2). The lower panel (B) shows the population-based distribution in Japan (from the Japan Society of Health Evaluation and Promotion 2002). The cholesterol level of US individuals is lower than that of the Japanese, yet CAD mortality is three times higher.

**Cholesterol-lowering medication and all-cause mortality: evidence against the presented statement based on the “reversal of causal relationship” hypothesis**

Harumi Okuyama (Kinjo Gakuin University)
In 2010, we published a book entitled “Cholesterol Guidelines for Longevity”, in which we presented evidence that high plasma cholesterol (total cholesterol or LDL-C) is associated with low cancer incidence and all-cause mortality, indicating that high cholesterol is a predictor of longevity (World Rev Nutr Diet 2011; 102: 124). The president of the Japan Atherosclerosis Society and the presidents of two other major medical societies immediately issued an official statement rejecting our cholesterol guidelines and stated that the high rate of all-cause mortality in the low cholesterol group is due to hepatic disorders and other causes, and that cholesterol-lowering medication does not increase but in fact decreases all-cause mortality, the so-called “reversal of causal relationship” hypothesis (Fig. 3) (http://dl.med.or.jp/dl-med/teireikaiken/20101020_1.pdf). In the present panel discussion, I pointed out that their statement

"Reversal of causal relationship" hypothesis by the presidents of three Japanese medical societies

**Fig. 3.** Schematic of the “reversal of causal relationship” hypothesis by the presidents of three major Japanese medical societies. The hypothesis implies that the high all-cause mortality in the low cholesterol group is due to hepatic diseases, cancer, and other conditions, and that cholesterol-lowering medication does not increase but decreases all-cause mortality. In the panel discussions, evidence against this hypothesis was presented.
was not based on evidence and that cholesterol-lowering medicines actually increase all-cause mortality. Our evidence was summarized as (1) cholesterol-lowering drugs (statins and clofibrate) increased cancer and all-cause mortality (Circ J 2002; 66: 1087), (2) the relative risks of high cholesterol for CHD varied from <1 to >5 among the examined populations, the variability of which was rationally accounted for by the proportion of FH in the groups (World Rev Nutr Diet 2007; 96: 1-168), (3) the reported side effects of statins included carcinogenesis, disorders of the central nervous system, and teratogenicity, and (4) the recommended lipid nutrition for the prevention of CHD is wrong in many aspects. Based on the evidence presented, I requested medical societies to change the direction of cholesterol-lowering medications.

We need Japanese evidence to assess the consequence of cholesterol lowering
Rokuro Hama, Japan Institute of Pharmacovigilance (Kusuri-no-Check)

The primary endpoint for the long-term effects of intervention in chronic disease should be “overall survival”, because other endpoints may conceal the adverse effects of the intervention (http://www.cancer.gov/cancertopics/pdq/levels-evidence-adult-treatment/HealthProfessional/page3). Evidence from studies conducted in Japan is needed for the assessment of intervention in Japanese people, because the spectrum of causes of death is very different between Japanese and Caucasian populations. Immune suppressants as cancer promoters are more important carcinogens than initiators. The significance of immune suppressants as carcinogens is indicated by the following phenomenon: many subjects have latent cancer; lymphocytes attack malignant cells; and cancer appears after depression of the immune system and disappears after an increase in immune function. Malignancies after transplantation are frequently diagnosed within 1 year and several (8–10) years or more after commencement of treatment with calcineurin inhibitors (potent immune suppressants). However, development of cancer between 1 and 8–10 years is very rare (Fig. 4). Hence, it is impossible to detect malignancies as adverse effects of statins through randomized controlled trials with follow-up periods of 5 years or less in which patients with malignancies observed within 6 months are excluded (e.g., the MEGA study). Statins decrease cell functions in general by inhibiting production of essential
components such as cholesterol, ubiquinone, and dolichol. Thus, they may impair cell function and induce organic changes in immune, nervous, and hormonal systems resulting in various diseases including infection, malignancies, and central and/or peripheral nervous system damage (*No medicine is necessary for cholesterol*. Kadokawa, Tokyo, 2006, in Japanese).

**Fig. 4.** Duration of calcineurin inhibitor use after cardiac transplantation and incidence rate of malignancies. Panel (a): Malignancies of all sites, and panel (b): Malignant lymphoma. Most of the malignancies appeared within 1 year and after several years; few occurred between these two time points (The Informed Prescriber 2010; 25: 50).

**Hypercholesterolemia is not a risk factor for all-cause mortality especially in Japanese women**

Tomohito Hamazaki (University of Toyama)

According to recent Japanese epidemiologic studies, all-cause mortality is low in subjects with high cholesterol levels compared with those with the lowest cholesterol levels. The only exception was the NIPPON DATA 80 study (*Atherosclerosis* 2007; 190: 216), which showed that all-cause mortality in subjects with cholesterol levels $\geq 260$ mg/dL was significantly higher than the control group (160–179 mg/dL). The data in this study were adjusted for serum albumin levels. This adjustment is theoretically incorrect because there is a significant positive correlation between serum levels of cholesterol and albumin (see above, Ogushi’s comment).
Adjustment for albumin decreases the favorable effects of cholesterol on mortality. In addition, the NIPPON DATA 80 study is likely to have recruited more participants with FH than in the general population in Japan because all participants were recruited from the National Cardiovascular Survey performed in 1980 (The Japanese Association for Cerebro-cardiovascular Disease Control, Report 1996, p269). Recently Tsuji (Arch Intern Med 2011; 171: 1121) found in a 10.9-year follow-up study with 16,461 participants in Moriguchi City that cardiovascular deaths were highest in the group with the lowest cholesterol levels (see Fig. 5).

![Fig. 5. Relationship between cardiovascular mortality and serum total cholesterol levels in Moriguchi City. A total of 16,461 citizens 15 years or older (about 75% female) were followed for a mean period of 10.9 years. The relative risk of cardiovascular mortality was calculated with adjustment for eight possible confounding factors. Coronary deaths are given as the ratio between the numbers of coronary and cardiovascular deaths (Arch Intern Med 2011; 171: 1121).](image)

**Summary**

Hamazaki and Okuyama

Almost all Japanese epidemiological studies showed that all-cause mortality was lower in subjects with high serum total or LDL-cholesterol levels. Studies showing the disadvantage of high cholesterol levels included or were likely to include more participants with FH than in the general Japanese population. This also explains why epidemiological studies with elderly people are not able to detect any disadvantage of high cholesterol levels; groups of elderly subjects contain a smaller proportion of vulnerable FH patients who die earlier than those...
Meta-analyses of the effects of statins were used to indicate the favorable effects of these drugs, which might be considered as proof that cholesterol has unfavorable effects. However, the absolute effect size of statins on all-cause mortality is rather small, if any. Moreover, studies included in meta-analyses of statins were performed before the new clinical research regulation came into effect in 2005–2006 in the EU, which required clinical trial results to be published even if the data were not favorable for the tested drugs (BJOG 2007; 114: 917, http://www.bjog.org/view/0/index.html). Considering the fact that placebo-controlled clinical trials performed after the new regulation were mostly negative (J Lipid Nutr 2010; 19: 65, http://www.jstage.jst.go.jp/article/ jln/19/1/65/_pdf/-char/ja/), the results published before the regulation were questionable and should not be used as the basis for recommendations for treatment with cholesterol-lowering medications.

Because the relative risks of high cholesterol for CHD vary from <1 to >5, administering cholesterol-lowering medications to all Japanese individuals equally is not rational; at least women and elderly men need to be carefully re-examined because no or little positive associations between plasma cholesterol and CHD mortality rates have been reported in these groups.