Towards a Paradigm Shift in Cholesterol Treatment

A Re-Examination of the Cholesterol Issue in Japan

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Challenging Plasma Cholesterol as a Risk Factor for Cardiovascular Disease

For many years a broad consensus has been established among researchers, health care professionals, medical-scientific societies and governmental bodies who agree that markedly elevated plasma concentrations of cholesterol and low-density lipoprotein (LDL) cholesterol are one among several other causal risk factors for increased occurrence of cardiovascular disorders [1–6]. Different pieces of evidence support a causal role of altered cholesterol metabolism in atherosclerosis development, including epidemiological observations and controlled trials, based primarily on dietary and drug interventions. More recently, studies relating genetic variation with cholesterol metabolism and health outcomes have added weight to the conclusion that elevated LDL cholesterol in plasma is a risk factor for the occurrence or cardiovascular disorders. Certain mutations of the gene encoding for proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme that is involved in cholesterol homeostasis induce both a reduced plasma LDL cholesterol and a lowered risk of coronary heart disease [7, 8]. In a large meta-analysis involving data from more than 300 000 people, a variety of genetic polymorphisms that induce lower plasma LDL cholesterol also reduce the risk of coronary heart disease, with a rather consistent reduction of the odds ratio by about 20% for each 0.25 mmol/l or 9.7 mg/dl lowered LDL cholesterol concentration [9]. These and other studies are based on the concept of 'Mendelian randomisation', an epidemiological method that assess the effects of genes considered randomly distributed in the population to obtain unbiased estimates of causation [10]. Moreover, effects of intervention studies provide rather convincing evidence. Several controlled intervention trials have achieved a proportional reduction of the rate of cardiovascular events along with the degree of lowering elevated LDL cholesterol that was reached [11–13]. In subjects with a markedly increased LDL cholesterol level due to a defective LDL cholesterol receptor function (familial hypercholesterolemia), cholesterol reduction with statins markedly improves the likelihood of event free survival [14]. Based on these and other pieces of evidence, health care professionals around the world treat individuals with primary genetic disorders that induce markedly increased LDL cholesterol plasma concentrations with the goal to reduce blood lipid levels as well as morbidity and mortality. For the general population dietary and lifestyle advice is provided that aims at reducing dyslipidemia and associated risks [5, 6]. However, it is not always adequately appreciated that cholesterol metabolism is only one piece of a complex and multifaceted puzzle of numerous determinants of risk, which also includes the level physical activity, obesity, adiposity, insulin resistance, smoking, different dietary variables e.g. the intake of omega-6 and omega-3 polyunsaturated fatty acids, and many others.

In this supplement, Tomohito Hamazaki and coworkers challenge the largely prevailing view and propose an ‘anti-cholesterol hypothesis’, which appears to be developed primarily from epidemiological observations in the Japanese population, with a number of further added arguments. This thoughtful proposal provides very stimulating reading material. The Editorial Board of the Annals of Nutrition and Metabolism favours the publication of controversial arguments and positions and supports open and unrestricted debates, which may provide the very basis of focussing arguments and of refining our scientific understanding. We wish to emphasize that content published in supplements of our journal is not peer reviewed under the supervision of the Editorial Board, but responsibility lies entirely with the guest editor of the respective supplement.

Berthold Koletzko
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