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# Prevention of Coronary Heart Disease

**From the Cholesterol Hypothesis to  $\omega$ 6/ $\omega$ 3 Balance**

Volume Editor

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**Abstract**

## **Prevention of Coronary Heart Disease From the Cholesterol Hypothesis to $\omega$ 6/ $\omega$ 3 Balance**

The cholesterol hypothesis established half a century ago proposed a health benefit in (1) reducing the intake of saturated FAs (S); (2) reducing that of cholesterol, and (3) increasing that of polyunsaturated FA (P) that was essentially linoleic acid (LA) in vegetable oils, to lower serum cholesterol (TC; a TC value of 1 mmol/l corresponds to 38.61 mg/dl) and thereby reduce atherosclerosis-related diseases. Following epidemiological studies on Greenland natives and Danes in the 1970s, basic and clinical studies have gradually convinced people to accept the effectiveness of seafood  $\omega$ 3 FAs for the prevention of coronary heart disease (CHD) so that (4) ‘increasing the intake of  $\omega$ 3 FAs’ is now additionally recommended in some countries. Nowadays, these four recommendations are widely adopted in the medical fields in many countries, although the amounts of seafood intake differ much among countries and populations. However, the cholesterol-lowering activity of high-LA vegetable oils was transient, and diet recommendations (1–3) were essentially ineffective in reducing TC values in the long run (>several years). We propose that feedback control mechanisms in the body cause traditional cholesterol biomarkers to have different importance in interventions of short-term and long-term duration. More importantly, the association of high TC values with high CHD mortality differs several-fold in some populations with no significant differences among other populations. The proportion of familial hypercholesterolemia (FH) in high TC groups seems to be a critical factor in the reported high CHD mortalities. High CHD mortality in high TC groups may simply reflect the incidence and severity of FH cases. Because of inborn disorders of LDL receptors and their metabolism, FH cases develop hypercholesterolemia at younger ages, develop CHD at >10 times higher rates, and die younger than in non-FH cases. As a result, lipid nutrition and pathology of CHD in FH cases should be studied separately from those for the majority of non-FH cases in most populations. An important observation in recent studies is that higher TC values associate with lower cancer and all-cause mortalities in general populations and aged populations in which the relative proportions of FH are likely to be low. Although the effectiveness of statins, cholesterol synthesis inhibitors, in preventing CHD has been accepted, the benefits of statins may be mediated not by lowering TC and LDL-C, but rather by suppressing the formation of

isoprenoid intermediates that have diverse activities. Furthermore, increased cancer and all-cause mortalities occurred in a Japanese intervention trial when a statin treatment lowered TC values from 264 to below 200 mg/dl. No benefit seems to come from efforts to limit dietary cholesterol intake or to lower TC values below approximately 260 mg/dl among general populations and aged populations ( $\geq 40$  years old in Japan and  $\geq 50$  years old in Austria). The cholesterol hypothesis regarded TC to be a mediator of disease that is increased by eating saturated fats and decreased by eating polyunsaturated fats. However, high TC can also be regarded as a biomarker for excessive mevalonate formation that accompanies excessive intakes of food calories which up-regulate gene expressions related to the levels of isoprenoid intermediates, cellular proliferation, carcinogenesis, inflammatory signaling mechanisms and unsuitable energy metabolism (chap. 1.4.). Biomarkers linearly linked to fatal CHD events need to be used in clinical epidemiology. In addition, an unbalanced intake of  $\omega 6$  over  $\omega 3$  polyunsaturated fats favors production of potent hormone-like eicosanoids whose actions lead to inflammatory and thrombotic lipid mediators and altered cellular signaling and gene expression which are major risk factors for CHD, cancers and shorter longevity (chap. 6.9.). High intakes of the  $\omega 6$  linoleic acid do not correlate linearly with mortality, but the resulting high proportions of  $\omega 6$  arachidonic acid in the highly unsaturated FAs of tissue lipids do correlate linearly with observed CHD fatalities. The health risk from high intakes of calories and saturated fats seems overcome by higher intakes of  $\omega 3$  FAs and lower  $\omega 6/\omega 3$  ratios in the diet. These favorable features are seen among Greenland and Mediterranean populations. Based on the data reviewed in this book, we recommend new directions of lipid nutrition for the primary and secondary prevention of CHD, cancer and all-cause deaths.