Prevention of Coronary Heart Disease
From the Cholesterol Hypothesis to ω6/ω3 Balance
Prevention of Coronary Heart Disease
From the Cholesterol Hypothesis to ω6/ω3 Balance

Volume Editor
Harumi Okuyama Nagoya

Authors
Harumi Okuyama Laboratory of Preventive Nutraceutical Sciences, Kinjo Gakuin University College of Pharmacy, Nagoya, Japan
Yuko Ichikawa Department of Health Promotion and Preventive Medicine, Nagoya City University School of Medical Sciences, Nagoya, Japan
Yueji Sun Department of Psychiatry, Dalian Medical University, Dalian, China
Tomohito Hamazaki Institute of Natural Medicine, University of Toyama, Toyama, Japan
W.E.M. Lands College Park, Md., USA

92 figures, 89 in color and 23 tables, 2007
Contents

IX  Abstract

Chapter 1
1  The Cholesterol Hypothesis – Its Basis and Its Faults
2  1.1. Cholesterol Hypothesis, Keys’ Equation and Key Concepts for New Interpretations
3  1.2. Current Nutritional Recommendations for the Prevention of Coronary Heart Disease Are Diverse among Scientists’ Groups
4  1.3. Effect of Dietary Cholesterol and P/S Ratio of Fatty Acids on Total Cholesterol – Short- and Long-Term Effects Differ
8  1.4. Dietary Saturated Fatty Acids, Polyunsaturated Fatty Acids and Cholesterol Are Positively Correlated with Age-Adjusted Relative Risk but Not with Multivariate Relative Risk for Myocardial Infarction
12  1.5. Increased Coronary Heart Disease Risk by Dietary Recommendations That Were Made Based on the Cholesterol Hypothesis

Chapter 2
19  Association of High Total Cholesterol with Coronary Heart Disease Mortality Differs among Subject Populations – Familial Hypercholesterolemia as a Key Concept
20  2.1. Characteristics of Familial Hypercholesterolemia
21  2.2. Epidemiological Studies Led to Different Conclusions for the Relationship between Total Cholesterol and Coronary Heart Disease
23  2.3. Data Rearranged to Convince Japanese People that High Total Cholesterol Is a Major Risk Factor for Coronary Heart Disease
27  2.4. The Association of Total Cholesterol with Coronary Heart Disease Differs among Different Age Groups, Which Is Likely to Be Correlated with Familial Hypercholesterolemia
31  2.5. Lipid Metabolism Is Likely to Differ Qualitatively between Familial Hypercholesterolemia and Hypercholesterolemic Non-Familial Hypercholesterolemia Cases, and the Observations in Familial Hypercholesterolemia Cases Should Not Be Extended Directly to Non-Familial Hypercholesterolemia

Chapter 3
37  Cancer and All-Cause Mortalities Are Lower in the Higher Total Cholesterol Groups among General Populations
39  3.1. Reports Showing Longer Survival in the Higher Total Cholesterol Groups Except for the Highest Total Cholesterol Group in Western Countries
42 3.2. A Large-Scale, Long-Term Follow-Up Study in Austria Demonstrated Age Group Differences in Mortalities
45 3.3. Reports on Japanese General Populations Showing Lower Mortalities from Cancer and All Causes in the Higher Total Cholesterol Groups
51 3.4. Interpretation of Reports on Korean, British and Japanese-American Men

Chapter 4

55 Pleiotropic Effects of Statins in the Prevention of Coronary Heart Disease – Potential Side Effects
56 4.1. Effectiveness of Statins for the Primary and Secondary Prevention of Coronary Heart Disease Proved in Western Countries
59 4.2. Potential Side Effects of Statins
62 4.3. Effectiveness of Statin Might Be Different in Japan Where People Eat Relatively Large Amounts of Seafood, and Coronary Heart Disease Events Are Roughly 1/4 of That of the USA
65 4.4. Side Effects of Statins and Socio-Economic Aspects of Statin Treatment

Chapter 5

67 Objective Measures of the Pathology of Coronary Heart Disease
69 5.1. Hisayama Study (Japan) in Which the Cause of Death Was Defined by Postmortem Examination
72 5.2. Pathobiological Studies of Americans in the PDAY Study
73 5.3. Pulse Wave Velocity Correlated Positively with Ischemic Changes in Electrocardiogram but Not with Total Cholesterol Levels
75 5.4. Angiograms Estimate Progression of Atherosclerosis That Was Independent of Total Cholesterol Values
76 5.5. Heart Rate Variability Measured with 24-Hour Holter Monitoring Relates to Risk for Coronary Heart Disease
77 5.6. Intima-Media Thickness Relates to Dietary Fatty Acids and 5-Lipoxygenase Genotype
81 5.7. Hypertension – Relationships to Coronary Heart Disease and Stroke

Chapter 6

83 ω3 Fatty Acids Effectively Prevent Coronary Heart Disease and Other Late-Onset Diseases – The Excessive Linoleic Acid Syndrome
84 6.1. Three Different Types of Highly Unsaturated Fatty Acid
86 6.2. Clinical Evidence that ω3 Fatty Acids Are Effective for the Primary and Secondary Prevention of Coronary Heart Disease
102 6.3. Recommendations to Decrease the Intake of Linoleic Acid (ω6) and Increase That of α-Linolenic Acid (ω3) and Oleic Acid (ω9) Were More Effective than Statin-Treatment for the Secondary Prevention of Coronary Heart Disease
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 (≥40 years old in Japan and ≥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 ω6 over ω3 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 ω6 linoleic acid do not correlate linearly with mortality, but the resulting high proportions of ω6 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 ω3 FAs and lower ω6/ω3 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.