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Low Serum Cholesterol Level and Increased Ischemic Stroke Mortality

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ifferent from coronary disease, which mostly results from coronary atherosclerosis with superimposed coronary thrombosis, stroke includes various pathological entities. Stroke includes not only ischemic and hemorrhagic stroke but also subtypes of ischemic stroke. The stroke-lipid connection would depend on the types and the subtypes of stroke. Reductions of stroke by cholesterol-lowering therapy have been documented in patients with previous stroke and those at high risk for coronary disease. However, these results seem to be based on predominance of atherothrombotic stroke over other subtypes of ischemic stroke in the study population, which shares a similar etiology with coronary disease.1,2

Whereas atherothrombotic stroke accounts for approximately one-half of ischemic strokes in Western populations,1 in the Japanese population it accounts for only approximately one-quarter of ischemic strokes, and cardioembolic stroke was more common than atherothrombotic stroke, accounting for 31% to 38% of ischemic strokes.2,3 As reported herein, the association of total cholesterol level with total ischemic stroke mortality was examined in a cohort of the general Japanese population, in whom the risk for coronary disease is very low and atherothrombotic stroke accounts for a lower proportion of ischemic strokes.

Methods. In Moriguchi City, Osaka, Japan, any citizen 15 years or older who did not receive another annual health examination covered by the Occupational Health and Safety Law or the School Health Law could receive the examination supported by national and local governments. The examination was performed as a mass health screening-style program targeting citizens without medical problems or a primary physician. The study population comprised 16,461 subjects who had an annual health examination in 1997, when the data started to be archived. Because those who underwent the examination mainly included self-employed people and their dependents, retirees, and dependents of employees who were not offered the examination by the employees’ companies, women predominated among the study subjects. The subjects were followed until the end of 2009. The cause of death was determined by the death certificates stored in the National Vital Statistics database sent from the Ministry of Health and Welfare. The underlying cause of death was coded according to the International Statistical Classification of Diseases, 10th Revision (ICD-10). Subjects who moved from Moriguchi City were treated as censored cases. The institutional review board of Kansai Medical University approved this study.

Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or the use of antihypertensive agents. Diabetes was defined as a nonfasting plasma glucose level of 200 mg/dL or higher (to convert to millimoles per liter, multiply by 0.0555), a fasting plasma glucose level of 126 mg/dL, or a history of diabetes. Smoking included only current smokers. A drinking habit was considered to be present if the subjects answered that they drank often or more frequently on the interview questionnaire.

The association between total cholesterol level and mortality was determined by dividing the subjects into 4 groups. Total cholesterol levels of 160 mg/dL, 200 mg/dL, and 240 mg/dL (to convert to millimoles per liter, multiply by 0.0259) were used as cutoff points. The relative risks were calculated with 95% confidence intervals for each end point of each subgroup relative to the lowest cholesterol category (<160 mg/dL) using a proportional hazards regression analysis with adjustment for age, sex, current smoker (yes/no), hypertension (yes/no), diabetes (yes/no), drinking habit (yes/no), and history of cardiovascular disease (yes/no). The statistical significance level was set at .05 (2 sided).
Results. During a mean follow-up of 10.9 years (median, 12.2 years), 1202 subjects died and 2243 subjects moved from Moriguchi City. Compared with subjects who did not move from Moriguchi City, they were younger (mean [SD] age, 48 [16] vs 55 [12] years) and included more women (78% vs 74%). There were 26% men (mean [SD] age, 54 [13] years), and the type of stroke varied with clinical characteristics (eTable; http://www.archinternmed.com).

Compared with the lowest cholesterol group (<160 mg/dL), the relative risks of ischemic stroke death were consistently and significantly lower in all other cholesterol groups after adjustment for clinical risk factors (Table). When aggressive cholesterol-lowering therapy is performed, increases in cardioembolic stroke and atrial fibrillation should be carefully monitored.

Table. The Results of the Multivariate Proportional Hazards Regression Analyses According to the Serum Cholesterol Level

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Cholesterol, mg/dL</th>
<th>&lt;160 (n=1275)</th>
<th>160-199 (n=5599)</th>
<th>200-239 (n=6487)</th>
<th>≥240 (n=3100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Deaths, No. (%)</td>
<td>34 (2.67)</td>
<td>99 (1.77)</td>
<td>115 (1.77)</td>
<td>45 (1.45)</td>
</tr>
<tr>
<td>Age- and sex-adjusted RR (95% CI)</td>
<td>1 [Ref]</td>
<td>0.55 (0.37-0.81)</td>
<td>0.49 (0.33-0.73)</td>
<td>0.45 (0.29-0.72)</td>
<td></td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1 [Ref]</td>
<td>0.52 (0.35-0.77)</td>
<td>0.46 (0.31-0.68)</td>
<td>0.42 (0.27-0.67)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>Deaths, No. (%)</td>
<td>16 (1.25)</td>
<td>37 (0.86)</td>
<td>43 (0.66)</td>
<td>13 (0.42)</td>
</tr>
<tr>
<td>Age- and sex-adjusted RR (95% CI)</td>
<td>1 [Ref]</td>
<td>0.43 (0.24-0.77)</td>
<td>0.36 (0.20-0.66)</td>
<td>0.25 (0.12-0.54)</td>
<td></td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1 [Ref]</td>
<td>0.40 (0.22-0.72)</td>
<td>0.33 (0.18-0.59)</td>
<td>0.23 (0.11-0.48)</td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>Deaths, No. (%)</td>
<td>10 (0.78)</td>
<td>18 (0.32)</td>
<td>19 (0.29)</td>
<td>9 (0.29)</td>
</tr>
<tr>
<td>Age- and sex-adjusted RR (95% CI)</td>
<td>1 [Ref]</td>
<td>0.36 (0.16-0.78)</td>
<td>0.28 (0.13-0.61)</td>
<td>0.31 (0.12-0.81)</td>
<td></td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1 [Ref]</td>
<td>0.34 (0.16-0.74)</td>
<td>0.26 (0.12-0.56)</td>
<td>0.29 (0.11-0.74)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>Deaths, No. (%)</td>
<td>6 (0.47)</td>
<td>13 (0.23)</td>
<td>13 (0.20)</td>
<td>1 (0.29)</td>
</tr>
<tr>
<td>Age- and sex-adjusted RR (95% CI)</td>
<td>1 [Ref]</td>
<td>0.39 (0.15-1.03)</td>
<td>0.30 (0.11-0.81)</td>
<td>0.05 (0.01-0.44)</td>
<td></td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1 [Ref]</td>
<td>0.36 (0.13-0.95)</td>
<td>0.25 (0.09-0.70)</td>
<td>0.04 (0.01-0.37)</td>
<td></td>
</tr>
<tr>
<td>Coronary</td>
<td>Deaths, No. (%)</td>
<td>7 (0.55)</td>
<td>29 (0.52)</td>
<td>41 (0.63)</td>
<td>15 (0.48)</td>
</tr>
<tr>
<td>Age- and sex-adjusted RR (95% CI)</td>
<td>1 [Ref]</td>
<td>0.77 (0.34-1.75)</td>
<td>0.83 (0.37-1.88)</td>
<td>0.71 (0.28-1.78)</td>
<td></td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1 [Ref]</td>
<td>0.73 (0.32-1.68)</td>
<td>0.80 (0.35-1.81)</td>
<td>0.67 (0.26-1.67)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; Ref, reference; RR, relative risk.
SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

a The RRs were calculated for each end point of each subgroup relative to the lowest cholesterol category (<160 mg/dL) using a proportional hazards regression analysis with adjustment for age, sex, current smoker, hypertension, diabetes, drinking habit, and history of cardiovascular disease.

b Hemorrhagic stroke does not include subarachnoid hemorrhage.

Comment. Although the subtypes of ischemic stroke in the present study were unknown, low total cholesterol level (<160 mg/dL) was associated with higher total ischemic stroke mortality after adjustment for clinical risk factors in a Japanese general population cohort.

Recent reports of the Hisayama study demonstrated that a lower low-density lipoprotein cholesterol level was associated with a lower incidence of atherothrombotic stroke. On the other hand, they reported a higher incidence of cardioembolic stroke at lower cholesterol levels. Several studies reported increased atrial fibrillation with a lower cholesterol level 3-7 independent of the thyroxin level. Therefore, the increase in total ischemic stroke mortality with a low cholesterol level observed in the present study possibly reflects an increase in cardioembolic stroke. A few studies reported associations of dietary or serum magnesium level with a low cholesterol level and increase in atrial fibrillation or ischemic stroke.8,9

When aggressive cholesterol-lowering therapy is performed, increases in cardioembolic stroke and atrial fibrillation should be carefully monitored.

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Online-Only Material: The eTable is available at http://www.archinternmed.com.


160 mg/dL) was associated with higher total ischemic stroke mortality after adjustment for clinical risk factors in a Japanese general population cohort.
Dietary Fiber Prevents Both Morbidity and Mortality From Respiratory Disease

We read with interest the recent finding by Park et al1 that dietary fiber was associated with a 69% and 54% lower risk of death from respiratory diseases among men and women, respectively, using data from the National Institutes of Health (NIH)-AARP prospective cohort. As indicated by the authors, anti-inflammatory properties of dietary fiber may contribute to the observed associations. Summarized herein are previously reported findings from 2 prospective cohorts, the Singapore Chinese Health Study (SCHS)2 and the US Atherosclerosis Risk in Communities (AIRC) study,3 that support a beneficial effect of higher fiber intake in the development of respiratory morbidity. In the SCHS, among 49,140 older adults, dietary fiber intake was inversely associated with incident cough with phlegm in a dose-dependent manner (adjusted odds ratio, 0.61 [95% confidence interval, 0.47-0.78]), comparing highest to lowest quartile of intake; P value for trend, <.001).2 In the AIRC study, higher fiber intake was significantly associated with better lung function (higher FEV1 [forced expiratory volume in 1 second], FVC [forced vital capacity], and FEV1/FVC).3 For example, FEV1 was 49 mL higher in the highest compared with the lowest quintile of cereal fiber intake (P value for trend, <.001). Higher cereal fiber intake was also related to lower prevalence of chronic obstructive pulmonary disease defined by spirometry (adjusted odds ratio, 0.79 [95% confidence interval, 0.64-0.98], comparing highest to lowest quintile of intake; P value for trend, .017).

In summary, previous prospective data from the SCHS and the AIRC study along with recent findings from the NIH-AARP study collectively support a beneficial effect of a diet high in fiber in preventing both morbidity and mortality from respiratory disease.

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See also page 1061

Number Needed to Treat: Implementation for Diets

Park et al concluded their study by stating that “A diet rich in dietary fiber may provide significant health benefit.”(pE7) Crowe et al2 recently reported their observations of the 519,978 men and women from the 10 European countries collaborating in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. They concluded in this large series that “participants consuming at least eight portions (80 g each) of fruits and vegetables a day had a 22% lower risk of fatal ischemic heart disease (IHD) compared with those consuming fewer than three portions a day.”(pE2)

See also page 1061

Considering the data provided by Crowe et al,2 one can calculate that the number needed to treat to avoid 1 death from IHD during 8.4 years is 500 (6.7 deaths per 1000 persons consuming <3 portions of fruits and vegetables per day vs 4.7 deaths per 1000 persons consuming 8 portions per day).2 One can also observe that, in 10 European countries, smoking behavior (addiction to tobacco, the first cause of both cancer and IHD) was more frequent than eating at least 8 portions of fruits and vegetables a day (24% vs 18%, respectively).

Public health strategies must first target the proven cost-effective measures to fight tobacco dealers and to help smokers to quit. The possible relation between fruit and vegetable consumption with IHD mortality is characterized by uncertainty. Moreover, adequate policies are still being sought for feasible long-term and even short-term populationwide changes in diet.