ORIGINAL CONTRIBUTION

Longitudinal Change in Serum Cholesterol Levels Among Isolated Hypertriglyceridemic Cases

Shu Kumagai1, Hiroshi Shibata1, Shuichiro Watanabe1, and Takao Suzuki2

The present study investigated longitudinal change in serum cholesterols of isolated hypertriglyceridemic cases (54 males, 34 females) and age-matched controls (115 males, 98 females) based on a 4-year longitudinal observation. At the baseline, the level of triglyceride was significantly higher in hypertriglyceridemic cases (329 ± 133 mg/dl in males, 274 ± 76 mg/dl in females) than in the controls (81 ± 18 mg/dl in males, 73 ± 16 mg/dl in females). Further, body mass index (BMI) was also significantly higher than that of the controls. There were no statistical differences in total cholesterol (TC) between the cases (197 ± 23 mg/dl males, 211 ± 30 mg/dl females) and the controls (189 ± 19 mg/dl males, 202 ± 18 mg/dl females). In hypertriglyceridemic cases, both TC and low density lipoprotein plus very low density lipoprotein cholesterols significantly increased between the baseline and the four years later (TC: 197 ± 23 mg/dl to 205 ± 26 mg/dl in males, p < 0.05, 211 ± 30 mg/dl to 227 ± 44 mg/dl in females, p < 0.01), whereas no change was observed in the controls. The BMI of the cases and the controls were unchanged throughout the study period. The present study shows that isolated hypertriglyceridemia with normocholesterolemia proceeds to hypercholesterolemia, which is compatible with endogenous lipoprotein metabolism. J Epidemiol, 1996; 6: 178-183.

Epidemiological studies have consistently shown a direct relationship of serum total cholesterol (TC) concentration on the incidence of and mortality from coronary heart disease1-6). On the other hand, the significance of elevated triglyceride (TG) level as a risk factor for coronary heart disease remains controversial7-36). A univariate analysis has shown a direct relationship between serum TG level and coronary heart disease6). However, prospective studies have not shown that TG level is an independent predictor for coronary heart disease after adjusting for confounding factors. Cambien et al.6 reported that an elevation of TG was a causal risk factor for coronary heart disease in normocholesterolemic subjects in the Paris Prospective Study. However, its mechanism has not been clarified. The Rancho Bernardo study17), using a 12-year follow-up of healthy men with a TC level of less than 240 mg/dl, did not show an association between hypertriglyceridemia and cardiovascular death.

Previous prospective studies have dealt with a relationship between TG level at baseline and an end point of coronary heart disease death in normocholesterolemic cases, but have not dealt with the changes in other individual lipids during the observation period. Metabolic studies on endogenous plasma lipids have indicated that the concentration of TG in plasma is dependent on the number of circulating very low density lipoprotein (VLDL) particles18). Serum TG and lipoprotein cholesterols are strongly biologically interrelated variables. Therefore, it is necessary to observe not only the level of serum TG cross-sectionally but also the change in serum cholesterol level according to TG level at baseline throughout the observation period. The present study investigated long-term longitudinal change in serum cholesterols among isolated hypertriglyceridemic cases with normocholesterolemia, compared...
SUBJECTS AND METHODS

Subjects of the present study were residents of Toda city ranging in age from 35 to 65 years old at baseline. Toda city lies in the southernmost area of Saitama Prefecture facing Metropolitan Tokyo. It has been developed as a residential area. Subjects for the present study were comprised of volunteers who underwent annual multiphasic health checkups from April 1984 through February 1988 as baseline, and responded to health checkups in Toda Municipal Health Care Center four years later. The mean of follow-up period was 4±0.4 years. So far 4590 residents (1671 males and 2919 females) underwent health checkups at baseline. During the baseline study period, four rounds of health checkups were carried out. Fifty-five percent of subjects underwent one or more checkups, of which the results from the first checkup were adopted for the present study. Those whose fasting serum TG was 200mg/dl or over at baseline were regarded as hypertriglyceridemic cases. Subjects having hypertriglyceridemia with functional disorder of liver (GPT≥35IU/L, or GOT≥40IU/L), hypercholesterolemia (low density lipoprotein plus very low density lipoprotein cholesterol [LDL+VLDL-C] ≥200mg/dl), impaired glucose tolerance (fasting blood sucrose ≥120mg/dl), or hyperuricemia (serum uric acid ≥8.0mg/dl) at baseline were excluded from the study. As isolated hypertriglyceridemic cases, 98 males and 58 females (total 156 cases) were qualified by above criteria at baseline period. Of these 156 cases, 54 males (55.1 percent) and 34 females (58.6 percent) were followed four years later. Controls were randomly selected from the group whose TG and LDL+VLDL-C were below 200mg/dl, and who were disease-free. Case-control pairs were matched one to two or more by sex and age. Table 1 shows the distribution of hypertriglyceridemic cases and age-matched controls by age-band and sex at baseline. Mean ages of cases and controls were 46.5±7.9 and 46.1±8.4 years old in males, 52.4±8.0 and 52.3±8.3 years old in females, respectively.

MEASUREMENTS

Twelve-hour fasting blood samples were taken from cubital veins on the morning of the health checkup day. Serum TG and TC were measured by enzymic method. High density lipoprotein cholesterol (HDL-C) was measured by combining dextran sulfate MgCl₂ precipitation and enzymic method 28. Precision control of measurements was carried out with a control serum (Moni-Trol, DADE, BAXTER) in the laboratory of Toda Municipal Health Care Center. Coefficients of variation were maintained in ranges 1.55-2.65% in TG, 0.35-0.81% in TC, 2.73-3.96% in HDL-C, throughout the study period. The value of LDL+VLDL-C was obtained from subtracting HDL-C from TC. Weight without jackets and height with shoes off were measured simultaneously.

RESULTS

The changes in serum lipids of cases and controls are summarized in Table 2. The mean level of TC was not significantly different between case-control at baseline. In hypertriglyceridemic cases, the level of TG was greater than 250mg/dl at the baseline and follow-up. Body mass index (BMI) was consistently higher in hypertriglyceridemic cases than in controls for both sexes. However, a change of BMI was observed neither in hypertriglyceridemic cases nor in controls. Hypertriglyceridemic females showed statistically significant elevation in TC, LDL+VLDL-C, and TC/HDL-C ratio (TC/HDL-C). On the other hand, HDL-C significantly declined in hypertriglyceridemic females. TC and LDL+VLDL-C levels significantly increased in hypertriglyceridemic males, too. Serum cholesterols were unchanged in controls throughout the study period. Figure 1 illustrates the

Table 1. Distribution of hypertriglyceridemic cases and their matched controls by sex and age-band at baseline, 1984-1988.

<table>
<thead>
<tr>
<th>Age-band</th>
<th>Males</th>
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<th></th>
<th></th>
<th>Females</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>Cases</td>
<td>Controls</td>
<td></td>
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</tr>
<tr>
<td>35-39</td>
<td>13 (24.1)</td>
<td>31 (26.9)</td>
<td>2 (5.9)</td>
<td>5 (5.1)</td>
<td></td>
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<tr>
<td>40-49</td>
<td>27 (50.1)</td>
<td>53 (46.1)</td>
<td>12 (35.3)</td>
<td>34 (34.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>9 (16.7)</td>
<td>20 (17.4)</td>
<td>12 (35.3)</td>
<td>32 (32.7)</td>
<td></td>
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<tr>
<td>60-65</td>
<td>5 (9.3)</td>
<td>11 (9.6)</td>
<td>8 (23.5)</td>
<td>27 (27.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>54 (100.0)</td>
<td>115 (100.0)</td>
<td>34 (100.0)</td>
<td>98 (100.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age*</td>
<td>46.5±7.9</td>
<td>46.1±8.4</td>
<td>52.4±8.0</td>
<td>52.3±8.3</td>
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</tbody>
</table>
* Mean ± standard deviation.
Table 2. Changes in mean serum cholesterol levels and body mass index of hypertriglyceridemic cases and their matched controls over 4 years according to sex, baseline at 1984-1988, follow-up at 1989-1993.

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Males</th>
<th>Females</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n=54)</td>
<td>Controls (n=115)</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>329 ± 133</td>
<td>298 ± 102</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>197 ± 23</td>
<td>205 ± 26</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>34 ± 9</td>
<td>35 ± 9</td>
</tr>
<tr>
<td>HDL+VLDL-C (mg/dl)</td>
<td>163 ± 22</td>
<td>170 ± 26</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>6.1 ± 1.3</td>
<td>6.2 ± 1.5</td>
</tr>
<tr>
<td>BMI</td>
<td>24.1 ± 2.8</td>
<td>24.3 ± 2.8</td>
</tr>
</tbody>
</table>

* : p<0.05  ** : p<0.01 (paired t-test).

TG denotes triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL+VLDL-C, low density lipoprotein cholesterol plus very low density lipoprotein cholesterol, expressed as subtracting HDL-C from TC; TC/HDL-C, TC to HDL-C ratio, expressed as the TC divided by the HDL-C; BMI, body mass index, expressed as the weight in kilograms divided by the square of height in meters.

changes of mean level in serum cholesterols and TC/HDL-C ratio between the baseline and follow-up among hypertriglyceridemic cases and controls according to sex.

**DISCUSSION**

High intraindividual variability of serum lipid levels often leads to the substantial bias in epidemiological studies. In particular, the intraindividual variation in TG value is considerable. There is a circadian variation which is mainly influenced by food intakes, 12-hour fasting is therefore an essential condition when collecting blood samples as carried out in the present study. Moreover, coefficients of variation on serum TG, TC and HDL-C measurements in the present were controlled in an acceptable range throughout the study period.

Several epidemiological and intervention studies have shown that change of BMI particularly influences serum TG. There is a circadian variation which is mainly influenced by food intakes, 12-hour fasting is therefore an essential condition when collecting blood samples as carried out in the present study. Moreover, coefficients of variation on serum TG, TC and HDL-C measurements in the present were controlled in an acceptable range throughout the study period.

Epidemiological studies have reported a significantly direct correlation between TG and BMI. The level of BMI in hypertriglyceridemic cases was higher than in controls in the present study. Therefore, overproduction of VLDL may directly lead to an elevation in serum TC level. Actually, the VLDL-C value is calculated as one-fifth of serum TG level following Friedewald formula. We consider that the elevation of serum TC in isolated hypertriglyceridemia during a 4-year period is compatible with the endogenous lipoprotein metabolism.

Epidemiological studies have reported a significantly direct correlation between TG and BMI. The level of BMI in hypertriglyceridemic cases was higher than in controls in the present study. Therefore, the lipoprotein metabolism under obesity is considered to be directed toward the elevation of TC and LDL+VLDL-C in hypertriglyceridemic cases as observed in the present study.

Hypertriglyceridemic females in this study also comprised subjects around the age of menopause. The community-based survey verified that serum cholesterol was higher in post-menopausal females than in premenopausal females. The change in concentrations of endogenous estrogens influences serum lipid and lipoprotein levels. Steep increase in cho-
Figure 1. Changes of mean levels in serum cholesterols and TC/HDL-C Ratio between baseline and follow-up among hypertriglyceridemic cases and their matched controls according to sex. 1 denotes mean level at baseline ; 2, at follow-up.
* p<0.05, ** p<0.01; Significant difference from baseline, paired t-test.

Figure 1. Changes of mean levels in serum cholesterols and TC/HDL-C Ratio between baseline and follow-up among hypertriglyceridemic cases and their matched controls according to sex. 1 denotes mean level at baseline ; 2, at follow-up.
* p<0.05, ** p<0.01; Significant difference from baseline, paired t-test.

Cholesterol in hypertriglyceridemnic females may be partly attributed to menopause during the study period. It should be noted that the elevation of serum cholesterol in hypertriglyceridemic cases was observed in both sexes. Therefore, in the present study the elevation of serum cholesterols is considered mainly to result from VLDL-C overproduction under continuation of an isolated hypertriglyceridemic condition.

BMI of our controls who were randomly selected from healthy subjects was lower than that of the level in National Nutrition Survey. Patterson et al. have shown that the concentration of plasma cholesterol increased by high dietary cholesterol in obese neonatal pigees but not in lean ones in an animal experiment. These data provide evidence that genetic differences between obese and lean bodies affect serum lipopro-
tein responses to dietary cholesterol intake. The elevation of cholesterol level found in isolated hypertriglyceridemic cases may result from the higher response to dietary cholesterol because of the higher BMI. Unfortunately, we were not able to learn whether the intake of cholesterol differed between two groups, since we did not investigate the nutrients intake of them.

The present study has shown that hypertriglyceridemia with normocholesterolemia could develop into hypercholesterolemia under continuation of the high level of BMI. Isolated hypertriglyceridemia should therefore be under surveillance from the standpoint of preventing coronary heart disease.

ACKNOWLEDGEMENTS

The present study is part of a research project, the Longitudinal Interdisciplinary Study on Aging by the Tokyo Metropolitan Institute of Gerontology (TMIG-LISA).

REFERENCES


