ORIGINAL CONTRIBUTION

Simple and Partial Correlations of Nutritional Factors to Serum High-Density Lipoprotein Cholesterol Levels in a Japanese Rural Population

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After determining the normal ranges of serum high-density lipoprotein cholesterol levels, correlates of HDL-cholesterol were analysed in a sample of 1,283 males and 2,123 females aged 40 years and older in an agricultural area of Shibata City, Niigata Prefecture. The distribution of serum HDL-cholesterol was nearly a log-scale normal distribution curve. The median and the lower and upper normal limits were calculated theoretically and the median values were: 40-49 age group, 51.9 mg/100 ml for males and 52.5 mg/100 ml for females; 50-59 age group, 52.5 and 51.4; 60-69 age group, 51.4 and 49.4; over 70 age group, 49.4 and 47.9. There was almost no difference in HDL-cholesterol levels between both sexes. This was explained as possibly due to alcohol intake raising HDL-cholesterol levels in males. There was a positive association of HDL-cholesterol levels with reported amount of alcohol intake in males. Inverse relationships were found between serum HDL-cholesterol levels and obesity in any age group for both sexes. An inverse correlation between percent energy contribution by carbohydrate and HDL-cholesterol was observed in males. Caloric intake was positively correlated to HDL-cholesterol in females.

HDL-cholesterol, alcohol intake, obesity, dietary intake, normal value

Cardiovascular disease epidemiologic studies have reported that serum high-density lipoprotein cholesterol (hereinafter referred to as HDL-cholesterol) is a protective factor against myocardial infarction^{1,3}. If the life-style and environmental factors that raise serum HDL-cholesterol levels are elucidated, primary prevention of coronary heart disease may be possible through control of these factors. Heretofore, however, there have been few studies which have examined the relationship between nutritional factors and serum HDL-cholesterol levels. This cross-sectional study was conducted for the purpose of examining that nutritional factors are related to serum HDL-cholesterol levels,

after determining the normal ranges of serum HDL-cholesterol levels of subjects aged 40 years and older who were engaged in agriculture in Shibata City, Niigata Prefecture, Japan.

SUBJECTS AND METHODS

Shibata City covers an area of 434 square kilometers and is located in the northern part of Niigata Prefecture. It includes a commercial residential area in the center and an agricultural area around it. For administrative convenience, the agricultural area is divided into eight districts. Four of these districts were inves-

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Table 1. Population, number responding and response rate

Sex	Age (year)	40-49	50-59	60-69	70-	Total
Males	Population eligible	438	616	475	307	1836
	Number responding*	263	394	385	241	1283
	Response rate (%)	60.0	64.0	81.0	78.5	69.9
Females	Population eligible	705	833	680	590	2808
	Number responding*	502	708	593	320	2123
	Response rate (%)	71.2	85.0	87.2	54.2	75.6

* number responding to both serum HDL-cholesterol measurement and dietary survey

tigated in this study. The population aged 40 years and over in these four districts were 2,567 males and 3,298 females of whom 1,836 males and 2,808 females were engaged in agriculture. Among these, 1,359 males and 2,246 females received health evaluations for cardiovascular disease at least once between 1981 and 1983. For this study, the following persons were excluded: those who refused to have blood samples taken, those whose serum HDL-cholesterol could not be measured because of incomplete separation of HDL due to high level of very low density lipoprotein, and those who were not able to complete the dietary survey because of hearing impairment, speech disturbance etc. After exculsion, a total of 1,283 males and 2,123 females remained in the study population (Table 1).

Using venous blood drawn without regard to the time of the previous meal, determination of serum HDL-cholesterol was made by the heparin-manganese chloride method following a standard approach, including analysis as recommended by the CDC⁹⁾. In order to maintain quality of control in serum HDL-cholesterol measurement, we participated in the CDC-NHLBI Lipid Standardization Program through the Osaka Prefectural Center for Adult Diseases. In this lipid standardization program, accuracy and precision for measuring low levels of cholesterol and HDL-cholesterol attained the permission criteria.

Histograms of serum HDL-cholesterol levels according to sex and age were developed and examined for type of distribution, and for determination of the statistical normal ranges.

Dietary and alcoholic intakes were assessed by a food frequency survey method which was newly designed by the authors⁵⁾. Dietitians interviewed subjects regarding food intake frequency, standard serving sizes of food and methods of preparation. The amount of nutrients and foods derived was presumed to be average long-term dietary intake, namely intake over the preceding year.

The degree of over- or under-weight was expressed as the percentage deviation of the actual level (M) from the standard level (S), $\Delta\% = (M - S)/S$. For this study, the standard weight was based on a table of

average weights by height and sex developed by Minowa et al⁶⁾. The body mass index, $BMI = (\text{body weight in kg}) \times 10^4 / (\text{height in cm})^2$, was also calculated. Subcutaneous skinfolds were measured with a calibrated caliper (National Institute of Health and Nutrition, Tokyo). Values for triceps and subscapular skinfolds were individually tabulated and later summed.

Smoking as a confounding variable between dietary intake and serum HDL-cholesterol was recorded as the average number of cigarettes per day.

The relationships between nutritional factors and serum HDL-cholesterol levels were studied with reference to simple and partial correlation coefficients. In order to have the partial correlation coefficients, in males, a multiple regression analysis was done with alcohol intake (per kg of body weight), carbohydrate intake (per kg of body weight), BMI and smoking as independent variables, taking into account their correlation to serum HDL-cholesterol levels and other nutritional factors.

In females, the same type of analysis was done with carbohydrate intake (per kg of body weight), animal fat intake (per kg of body weight) and BMI and independent variables. For statistical analysis, the SAS statistical package was used.

Figure 1. Histogram of Serum High-Density Lipoprotein Cholesterol Distribution in 708 females aged 50 to 59 years.

RESULTS

Statistical normal ranges of serum HDL-cholesterol

Percent frequency histograms of serum HDL-cholesterol were developed for age and sex. For the sample shown in Figure 1, a distribution closely similar to log-scale normal distribution was suggested. Therefore, HDL-cholesterol values were transformed into logarithms, and the cumulative percent frequency was plotted on a normal probability sheet, the results of which indicated that the distribution of serum HDL-cholesterol was nearly a log-scale normal distribution.

The statistical normal ranges of serum HDL-cholesterol were obtained by the following method⁷⁾. Using X transformed into logarithms from serum HDL-cholesterol values, X and S were calculated,

$$X = \sum X_i / n, S = \sqrt{\sum (X_i - X)^2 / n - 1}.$$

Using initial ranges between $X - 3S$ and $X + 3S$, the data beyond this range were then excluded, and mean (X') and standard deviation (S') were recalculated. The values X' , $X' \pm 2S'$, and $X' \pm S'$ transformed inversely into their original ones were defined as median, the range of 95% distribution, and the range of 68% distribution, respectively.

The results of the defined medians, the ranges of 95% distribution and those of 68% distribution of serum HDL-cholesterol classified by sex and age are shown in Table 2. The median tended to decrease slightly with age, and this tendency was more pronounced in females than in males. When the subjects aged 40-49 years were excluded, the median was higher in males than in females.

Association of nutritional factors with serum HDL-cholesterol levels

The simple correlation coefficients between nutritional factors and serum HDL-cholesterol levels are shown in Table 3-1 for males and Table 3-2 for

females. In male subjects, alcohol intake and percent of total energy intake contribution by alcohol were positively and significantly correlated to serum HDL-cholesterol levels. Relative weight, BMI and subcutaneous skinfolds were inversely and significantly correlated to HDL-cholesterol. While a significant inverse correlation between percent energy contribution by carbohydrate and HDL-cholesterol was shown, a significant correlation between carbohydrate intake and HDL-cholesterol was not found.

In female subjects, a significant inverse correlation between relative weight, BMI or subcutaneous skinfolds and HDL-cholesterol was seen except for the age group of 40-49 years. The correlation between total energy intake and HDL-cholesterol was also observed. The correlation of major nutrients such as animal protein, animal fat, vegetable fat, iron and calcium to HDL-cholesterol was statistically significantly positive, but not in all age groups.

Results from the multiple regression analysis were shown in Table 4-1 for males and Table 4-2 for females. In males, the partial correlation coefficients for alcohol intake and BMI were statistically significant. The coefficient between smoking and HDL-cholesterol was inverse, but it reached statistical significance only in the age groups of 40-49 and 60-69 years.

In females, the partial correlation coefficient for BMI reached statistical significance in all age groups. The coefficient for animal fat was positive and statistically significant in females aged 40-49 years and 70 years or over.

DISCUSSION

With the understanding that comparison of median and mean of serum HDL-cholesterol levels of Shibata City with other intra- and inter-country data must be interpreted carefully, because of differences in measuring method, particularly the method of HDL separation, and the state of quality control among the labora-

Table 2. The level of serum HDL-cholesterol by sex and age in an agricultural area of Shibata City, Niigata Prefecture (mg/100 ml)

Sex	Age (year)	Mean $\pm$ S.D.	Median	95% range	68% range
Males	40-49	53.2 $\pm$ 13.8	51.9	30.2-89.1	39.6-68.0
	50-59	53.5 $\pm$ 15.1	52.5	28.2-97.5	38.5-71.5
	60-69	52.7 $\pm$ 14.9	51.4	28.7-91.8	38.5-68.7
	70-	50.5 $\pm$ 13.8	49.4	28.2-86.4	37.3-65.4
Females	40-49	53.5 $\pm$ 12.1	52.5	33.1-83.0	41.7-66.0
	50-59	52.4 $\pm$ 12.9	51.4	30.5-86.4	39.6-66.7
	60-69	50.8 $\pm$ 13.7	49.4	28.2-86.4	37.3-65.4
	70-	48.9 $\pm$ 12.6	47.9	28.5-80.6	37.0-62.2

Table 3-1. Correlation coefficients between nutritional factors and serum HDL-cholesterol in males

Age	40-49	50-59	60-69	70-
No. of samples	263	394	385	241
Nutrient (per kg of body weight)				
Energy	0.190	0.193	0.150	0.182
Carbohydrate	0.085	0.027	-0.026	0.026
Animal protein	0.085	0.146	0.130	0.115
Vegetable protein	0.115	0.094	0.039	0.115
Animal fat	0.051	0.061	0.129	0.120
Vegetable fat	-0.061	0.082	0.066	0.123
Iron	0.079	0.133	0.091	0.110
Calcium	0.112	0.042	0.067	0.090
Salt	0.100	0.064	0.071	0.032
Alcohol	0.313*	0.328*	0.325*	0.308*
Food (per kg body weight)				
Cereal	0.152	0.044	0.017	0.036
Rice	0.145	0.074	0.019	0.014
Potato	-0.005	0.040	0.054	-0.015
Sugar	-0.071	-0.117	0.000	-0.082
Confectionery	-0.092	-0.057	-0.164	0.027
Oil and fat	-0.033	0.057	0.109	0.089
Miso (soy bean paste)	0.008	0.028	-0.008	0.033
Pulses other than miso	0.024	0.053	0.053	0.105
Fish	0.065	0.097	0.129	0.030
Meat	-0.027	0.140	0.072	0.027
Egg	0.151	0.125	0.149	0.209
Milk	0.076	-0.042	0.032	0.034
Fresh vegetable	0.052	0.149	0.117	0.100
Salted vegetable	-0.005	0.033	0.013	-0.080
Fruits	-0.047	-0.001	0.001	0.013
Seaweed	-0.027	0.015	0.129	0.138
Milk drinks, fruit drinks and carbonated beverages	-0.031	-0.002	0.028	-0.110
Caloric percent of				
Carbohydrate	-0.147	-0.228*	-0.279*	-0.274*
Animal protein	-0.028	-0.001	0.062	0.026
Vegetable protein	-0.125	-0.138	-0.182	-0.169
Animal fat	-0.031	-0.060	0.064	0.052
Vegetable fat	-0.199	-0.042	-0.006	0.081
Alcohol	0.267*	0.299*	0.292*	0.250*
Anthropometry				
Relative weight	-0.251*	-0.251*	-0.333*	-0.163
BMI	-0.252*	-0.248*	-0.328*	-0.157
Skinfold thickness	-0.204*	-0.248*	-0.258*	-0.187
Upper arm circumference	-0.186	-0.078	-0.220*	-0.155

* $p < 0.05$

tories (Some laboratories were not participants in the CDC-NHLBI program.), serum HDL-cholesterol levels for Shibata City were compared (Figure 2)⁸⁻²⁴).

The solid lines in Figure 2 indicate populations in Japan and broken lines represent those of Western countries. In male subjects, the levels for Shibata City were positioned near the average or above. In general, the levels for Japanese populations were higher

than those of Western countries, and were especially higher in Akita prefecture where the death rate from stroke is high even in Japan. The ratio of HDL-to-total-cholesterol in Japan is probably high in view of serum total cholesterol levels in Japan being much lower than those in Western countries.

On the other hand, in female subjects, the HDL-cholesterol levels for Shibata City were lower as shown

Table 3-2. Correlation coefficients between nutritional factors and serum HDL-cholesterol in females

Age	40-49	50-59	60-69	70-
No. of samples	502	708	593	320
Nutrient (per kg of body weight)				
Energy	0.144	0.201*	0.204*	0.260*
Carbohydrate	0.075	0.153	0.130	0.195
Animal protein	0.211*	0.153	0.166	0.210*
Vegetable protein	0.070	0.199	0.194	0.192
Animal fat	0.174	0.147	0.173	0.257*
Vegetable fat	0.166	0.177	0.195	0.206*
Iron	0.139	0.203*	0.197	0.191
Calcium	0.140	0.179	0.214*	0.221
Salt	0.058	0.154	0.110	0.120
Alcohol	0.064	0.077	0.163	0.099
Food (per kg of body weight)				
Cereal	0.046	0.143	0.095	0.137
Rice	0.035	0.107	0.030	0.129
Potato	0.012	0.141	0.102	0.072
Sugar	0.053	0.069	0.112	0.218
Confectionery	0.018	0.017	0.082	0.082
Oil and fat	0.135	0.127	0.116	0.161
Miso (soy bean paste)	0.003	0.146	0.123	0.103
Pulses other than miso	0.073	0.200	0.177	0.186
Fish	0.139	0.110	0.094	0.172
Meat	0.161	0.070	0.102	0.042
Egg	0.114	0.162	0.154	0.177
Milk	0.085	0.099	0.125	0.176
Fresh vegetable	0.070	0.158	0.123	0.112
Salted vegetable	0.036	-0.009	0.015	-0.017
Fruits	0.097	0.074	0.106	0.056
Seaweed	0.049	0.084	0.055	0.121
Milk drinks, fruit drinks and carbonated beverages	0.089	0.002	-0.043	-0.026
Caloric percent of				
Carbohydrate	-0.148	-0.064	-0.152	-0.123
Animal protein	0.130	-0.005	0.044	0.067
Vegetable protein	-0.114	-0.001	-0.028	-0.116
Animal fat	0.093	0.024	0.092	0.156
Vegetable fat	0.097	0.049	0.081	0.034
Alcohol	0.076	0.065	0.164	0.079
Anthropometry				
Relative weight	-0.196	-0.317*	-0.246*	-0.303*
BMI	-0.199	-0.313*	-0.250*	-0.302*
Skinfold thickness	-0.083	-0.242*	-0.143	-0.274*
Upper arm circumference	-0.138	-0.190	-0.175	-0.317*

* $p < 0.05$

in Figure 2, and levels for Japanese populations were lower than those of Western countries. Although in Western countries the difference in HDL-cholesterol levels between both sexes are large, levels for females being higher than for males, there was almost no difference between both sexes in the Japanese populations, including Shibata City. This has been explained as possibly due to alcohol intake raising

HDL-cholesterol levels in male subjects.

In summary, the results of analysis of simple and partial correlations between nutritional factors and serum HDL-cholesterol levels in this study indicated that there were relatively strong relationships between HDL-cholesterol levels and alcohol intake in male subjects. In females, however, the relationship between HDL-cholesterol levels and alcohol intake

Table 4-1. Partial correlation coefficients between selected independent variables and serum HDL-cholesterol in males

Age (years)	40-49	50-59	60-69	70-
Alcohol (g/body weight•kg)	0.323**	0.327**	0.282**	0.305**
Carbohydrate (g/body weight•kg)	0.005	-0.007	-0.145*	-0.095
BMI	-0.197*	-0.218**	-0.352**	-0.205**
Smoking (cigarettes/day)	-0.162*	-0.142	-0.106**	-0.086

*: $p < 0.05$ **: $p < 0.01$ **Table 4-2.** Partial correlation coefficients between selected independent variables and serum HDL-cholesterol in females

Age (years)	40-49	50-59	60-69	70-
Carbohydrate (g/body weight•kg)	-0.046	-0.009	-0.004	-0.012
Animal fat (g/body weight•kg)	0.126*	0.070	0.099	0.186*
BMI	-0.157*	-0.257**	-0.232**	-0.207**

*: $p < 0.05$ **: $p < 0.01$ **Figure 2.** International Comparison of the level of Serum High-Density Lipoprotein Cholesterol by age and sex. —: Populations in Japan, ----: Populations in the U.S. and European countries. Figure at each line: Reference number.

could not be analysed as there were only 22 habitual drinkers among the 2,123 female subjects in Shibata City at that time.

From the results of Lipid Research Clinics Program Prevalence Study²⁵⁾, Cooperative Lipoprotein Phenotyping Study³⁾, and National Health and Nutrition Examinations Survey II²³⁾ in the U.S., the association of alcohol intake with serum HDL-cholesterol level was strong. Similar relationships to alcohol intake were reported for cross-sectional studies in Japan also^{11,24)}.

Experimentally it was shown that increasing alcohol intake for long durations raised serum HDL-cholesterol levels^{26,27)}. The main subfractions of human HDL are HDL₂ and HDL₃. Haffner et al. reported no relationship between alcohol consumption and HDL₂-cholesterol, but a positive and strong correlation to HDL₃-cholesterol²⁸⁾. According to a study by Taskiran et al., moderate habitual intake of less than 40 g/day of alcohol increased the concentration HDL₃ particles²⁹⁾. An alcohol loading test showed decreases in serum HDL₂-cholesterol and increases in HDL₃-cholesterol³⁰⁾. Johansson et al.³¹⁾ found that about 30 percent of alcoholics showed elevation of serum HDL-cholesterol levels, but stated that the composition of this elevated HDL-cholesterol might differ from that of normal HDL-cholesterol. This conclusion is based on the separation of HDL-cholesterol by agarose-gel electrophoresis and antigen-antibody crossing electrophoresis, where electrophoretic patterns of HDL-cholesterol in alcoholics were different from those in healthy persons. Danielsson et al.³²⁾ reported that patterns of HDL-cholesterol elevation by alcohol intake varied such as elevation by HDL₂-cholesterol alone, and elevation of both HDL₂- and HDL₃-cholesterol, and in an ultra-centrifugal separation, a narrow and asymmetric band of HDL₂-cholesterol sometimes appeared, or a broad and symmetric HDL₂-cholesterol were found out. In addition, in the examination of the composition of the lipid and the protein, it was reported that three patterns were found as follows: increases in apolipoprotein of HDL, increases in cholesterol of HDL, and increases in both. Thus, habitual alcohol drinking can raise serum HDL-cholesterol levels, but it may be appropriate to view this elevation as being accompanied by changes in its substance.

Evidences that habitual drinking is one of the environmental causes of hypertension have been accumulating recently³³⁻³⁶⁾. Since hypertension is a strong risk factor for ischemic heart disease and stroke, the effect of alcohol intake on serum HDL-cholesterol levels must be examined within the context that blood pressure levels are also affected by alcohol intake.

Serum HDL-cholesterol levels correlated inversely to relative weight, BMI and skinfold thickness in our present study. Similar inverse correlations between HDL-cholesterol and obesity were epidemiologically found in several studies reported by LRC Study Group³⁷⁾, Rhoads et al.¹⁾, Carlson et al.¹⁹⁾, and others^{11,23,24,38,39)}. In a study of 250 pairs of monozygotic twins ranging in age from 42 to 55 years, researchers found that for an average increase of BMI of 7.3%, there was a 4.9% decrease in HDL-cholesterol⁴⁰⁾. In obese women, intra-abdominal (waist-to-hip ratio) fat accumulation, independent of total fat, was associated with significantly lower serum HDL-cholesterol⁴¹⁾. In addition, it was reported that weight reduction intervention to prevent coronary heart disease resulted in elevation of HDL-cholesterol^{39,42)}.

Hypertriglyceridemia is often found in the obese. Influx of triglyceride-rich lipoprotein into the blood stream is normal or elevated in hypertriglyceridemia, and lipoprotein lipase activities are often suppressed, resulting in decrease in the synthesis of HDL by the pathway from VLDL to HDL and a lowering of serum HDL-cholesterol levels^{43,44)}. Even in the case where the activity of lipoprotein lipase is normal, the influx of free cholesterol, phospholipids and apolipoproteins into HDL increases when the influx of triglyceride-rich lipoprotein is activated. The HDL particles become saturated with lipids and apolipoproteins, and become unstable, accelerating the catabolism of HDL and consequently leading to reduced serum HDL-cholesterol levels.

For nutritional factors other than alcohol and obesity, energy percentage from carbohydrate inversely and weakly correlated to serum HDL-cholesterol in males. In LRC's investigation²⁵⁾, the amount of carbohydrate, sugar and starch taken also correlated inversely and weakly to HDL-cholesterol. The mechanism of this process was unclear.

In females, serum HDL-cholesterol levels correlated inversely to obesity, and positively but weakly to energy intake. Need for future investigation regarding the relationship energy intake and expenditure to HDL-cholesterol is indicated. According to the US-Canada Collaborative Study⁴⁵⁾, physical activity as a daily habit positively correlated to HDL-cholesterol independent of other factors. A study indicated that adults who walked for exercise from 2.5 to 4.0 hours or more each week tended to have a 3.4% increase in HDL-cholesterol level than subjects who did not walk regularly⁴⁶⁾. There are some reports that serum HDL-cholesterol levels in track and field athletes and skiers are higher than those in non-athlete controls^{47,48)}, that participants in a 1-year running program showed an increase in HDL-cholesterol and HDL₂ mass concen-

trations more than control subjects⁴⁹), and that HDL-cholesterol in sedentary workers tended to be low⁵⁰), but with training exercise serum HDL-cholesterol levels could be raised⁵¹⁻⁵³). Brisk walking for 1 year by previously sedentary women for an average of 155 minutes per week resulted in an increase of 27% in HDL-cholesterol level compared with a 2% increase in control subjects⁵⁴). Thus, relatively consistent strenuous exercise appears to increase the concentration of HDL-cholesterol in serum.

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