So-called "common mutations" have been described in Japanese patients with FH, CETP deficiency and LPL deficiency. It has been reported that in patients with CETP deficiency (activity) < 75% of control), 65.7% had one of the 2 common mutations (1,451 + 1G > A and D442G) or both, and that in patients with marked HALP (HDL-cholesterol > 100 mg/dl), 57.5% had at least one of these common mutations (25), suggesting that genetic diagnosis could be feasible in CETP deficiency. On the other hand, prevalence of common mutations in the LDLR gene is relatively low (3, 4), indicating that genetic diagnosis of patients with FH may not be feasible.

FCHL is speculated to be the most prevalent disorder in genetic hyperlipidemia, however, the molecular mechanism has not been clarified. Similarly, the cause of FH-like syndrome, characterized by hypercholesterolemia, premature atherosclerosis and tendon xanthoma without reduction in LDLR activity, is also unknown. Further investigation should be performed to elucidate the molecular mechanisms of such disorders.

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Journal of Atherosclerosis and Thrombosis Vol. 11, No. 3
Original Articles

Clinical Features of Familial Hypercholesterolemia in Japan in a Database from 1996–1998 by the Research Committee of the Ministry of Health, Labour and Welfare of Japan

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Familial hypercholesterolemia (FH) is one of the most common primary hyperlipidemias, characterized by a heterozygous or homozygous phenotype for a severe serum low-density lipoprotein (LDL)-cholesterol level and advanced atherosclerosis, leading to coronary artery diseases (CAD). Various kinds of mutations in the LDL receptor gene responsible for the genetic disease have been identified since the human LDL receptor gene has been identified. In this study, the clinical features of FH were investigated using a database based on nationwide surveillance for primary hyperlipidemia and related disorders by the Research Committee on Primary Hyperlipidemia. The clinical features and the frequencies of accompanying vascular diseases in 660 cases of FH homozygotes and heterozygotes showed that the incidence of CAD was negatively associated with plasma HDL-cholesterol levels, but not with plasma LDL-cholesterol levels, in 641 FH heterozygotes. Risk factor analyses revealed that hypertension, male, smoking, low HDL-cholesterol levels, age > 50 y, diabetes mellitus, and hypertriglyceridemia were positive risk factors for CAD. The summarized gene analysis in FH heterozygotes showed at least 4 mutations in the LDL receptor gene as common mutations in Japan. The average serum lipids and frequency of CAD based on each common mutation suggested that their clinical features are in part determined by responsive mutations in the LDL receptor gene. ***J Atheroscler Thromb, 2004; 11: 146–151.***

Key words: Database, LDL receptor, Mutation, Heterozygote

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Introduction

Various gene abnormalities causing primary hyperlipidemia have been identified in our country. Surveillance for the current gene analysis has been started by the Research Committee on Primary Hyperlipidemia (Chairperson: Professor Toru Kita, Kyoto University), organized

by the Ministry of Health, Labour and Welfare in 1996 (1).

Familial hypercholesterolemia (FH) is one of most frequent primary hyperlipidemias. The underlying gene abnormalities have been identified on the low-density lipoprotein (LDL) receptor gene locus. A previous investigation based on the database created by the Research Committee on Primary Hyperlipidemia reported that approximately 80 mutations have been identified in various regions in the LDL receptor gene in Japan, and some of them may be more prevalent than others, comprising the so-called "common mutations" (2–4). Furthermore, the possibility of different responses of mutations against cholesterol-lowering therapy was suggested in FH (5). In this study, the clinical features of FH in Japan were investigated using the above database for mutations in Japanese patients with primary hyperlipidemia and related disorders. Additionally, the clinical phenotypes in FH with the common mutations were studied using three databases based on different areas in Japan.

Methods

The database for mutations in Japanese patients with primary hyperlipidemia and related disorders by the Research Committee on Primary Hyperlipidemia organized by the Ministry of Health, Labour and Welfare was used for the analysis in this study (2–4). The analyses of phenotypes for the common mutations were performed based on the databases provided by Drs. Maruyama and Yamashita (Osaka University), Drs. Kajinami and Mabuchi (Kanazawa University) and Drs. Bujo and Saito (Chiba University). The results are shown as mean ± SD for each index. Comparison of data was performed using the Student's *t*-test and/or ANOVA, and a value of $p < 0.05$ was considered significant. Logistic analyses were performed to obtain odds ratios for coronary artery disease (CAD).

Results

Clinical profile of familial hypercholesterolemia in Japan

The clinical features of 660 registered cases of FH (19 cases of homozygotes including two compound heterozygotes, and 641 cases of heterozygotes) were analyzed (Table 1). Both in homozygotes and heterozygotes, more women were registered than men (63% and 54%, respectively). The average age of cases for homozygotes and heterozygotes was 26 y (4–49 y) and 51 y (1–85 y), respectively. The average serum total cholesterol (TC) and LDL-cholesterol (LDL-C) of homozygous FH was 686 mg/dl and 582 mg/dl, respectively. The average serum TC and LDL-C of heterozygous FH was 324 mg/dl and 248 mg/dl, respectively. The proportion of type IIb hyperlipidemia in the WHO classification, which indicates hypertriglyceridemia as well as hypercholesterolemia, was 22% for homozygotes and 23% for heterozygotes. The serum high density lipoprotein-cholesterol (HDL-C) level was 35 mg/dl in homozygotes.

The occurrence of arcus cornea was 85% in homozygotes and 38% in heterozygotes. Tendon xanthoma was observed all in homozygotes and in 82% of heterozygotes. The occurrences of skin xanthoma were not as frequent as those of tendon xanthoma: 13% in homozygotes and 8% in heterozygotes. The occurrences of xanthelasma were 31% in homozygotes and 9% in heterozygotes. There was a history of CAD in 73% of homozygotes and 24% of heterozygotes. Other atherosclerotic diseases, cerebrovascular diseases (CVD) and arteriosclerosis obliterans (ASO), were not observed in homozygotes, and observed at 3% and 2% in heterozygotes, respectively.

Serum lipids and CAD in heterozygous FH

In heterozygous FH, the clinical profiles of the 296 male cases were compared with those of the 345 female cases (Table 2). The average age of the male and female cases was 49 y and 54y, respectively. The average body mass index (BMI) of the male and female cases was 23.5 kg/m^2 and 22.6 kg/m^2, respectively. The average serum cholesterol levels of heterozygous FH were not significantly different between the males and females. The TG and

Table 1. Clinical features of FH in Japan.

	Homozygotes	Heterozygotes
n	19 (2:comp.hetero)	641
Sex (M/F)	7/12	296/345
Age (y)	26 ± 14 (19)	51 ± 15 (548)
BMI (kg/m^2)	17.2 ± 3.3 (8)	23.0 ± 3.3 (566)
TC (mg/dl)	686 ± 250 (19)	324 ± 71 (568)
LDL-C (mg/dl)	582 ± 132 (15)	248 ± 67 (512)
TG (mg/dl)	157 ± 117 (17)	132 ± 85 (551)
HDL-C (mg/dl)	35 ± 21 (16)	47 ± 14 (517)
IIa/IIb	14/4	430/130
Arcus cornea (%)	85% (13)	38% (498)
Xanthoma (%)	100% (16)	87% (556)
Xanthelasma (%)	31% (16)	9% (556)
Skin (%)	13% (16)	8% (556)
Tendon (%)	100% (16)	82% (556)
CAD (%)	73% (15)	24% (538)
CVA (%)	0% (3)	3% (477)
ASO (%)	0% (3)	2% (475)

Mean ± SD, Numbers in parentheses show the cases for analysis.

HDL-C levels were significantly higher in the males than in the females; the proportion of type IIb hyperlipidemia was higher in the males than in the females. There were no significant differences between the males and females in the occurrence of arcus cornea, skin xanthoma, or tendon xanthoma.

Figure 1 shows the relationships between serum lipids and occurrence of CAD in heterozygous FH. There was no obvious relationship between TC, LDL-C or triglyceride (TG), and CAD occurrence. However, the occurrence was most frequent in cases with LDL-C of more than 320 mg/dl or TG of more than 250 mg/dl. Notably, there was a clear negative tendency in the relationship between CAD occurrence and HDL-C; an increased HDL-C level was associated with a decreased CAD occurrence, and the occurrence at an HDL-C level of more than 60 mg/dl was reduced to about one-fifth of that at less than 35 mg/dl.

Males with FH showed a significantly higher occurrence of CAD than females (Fig. 2). There was no significant difference in CVD occurrence. Males with FH showed a higher tendency of occurrence of ASO than females, although not significant by. Further analysis of the heterozygotes was performed separately for type IIa and IIb hyperlipidemia, in order to determine the significance of accompanying hypertriglyceridemia for the occurrence of CAD (Fig. 3). There was no significant difference in CAD occurrence between the two types in the males. In the females, the cases with type IIb showed an obviously increased CAD occurrence compared to the cases with

Table 2. Clinical features of FH heterozygotes in Japan.

	Males	Females
n	296	345
Age (y)	49 ± 13 (244)	54 ± 16 (304)
BMI (kg/m²)	23.5 ± 3.3 (260)	22.6 ± 3.2 (306)
TC (mg/dl)	324 ± 70 (261)	325 ± 72 (307)
LDL-C (mg/dl)	249 ± 132 (261)	248 ± 69 (279)
TG (mg/dl)	153 ± 99 (256)	114 ± 65 (295)**
HDL-C (mg/dl)	42 ± 12 (237)	50 ± 15 (280)**
IIa/IIb	179/81	230/49*
Arcus cornea (%)	40% (229)	36% (269)
Xanthoma (%)	88% (254)	88% (302)
Xanthelasma (%)	6% (254)	10% (302)
Skin (%)	11% (254)	10% (302)
Tendon (%)	82% (254)	83% (302)

Mean ± SD, Numbers in parentheseis show the cases for analysis.
**: $p < 0.001$, *: $p < 0.0001$, vs male

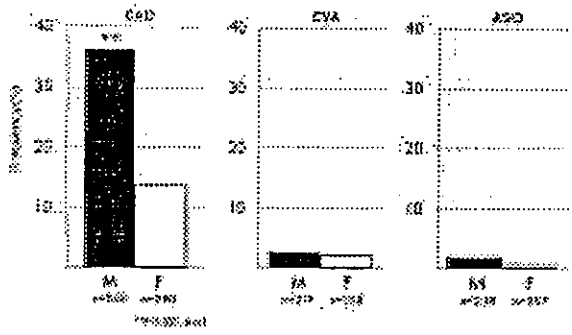

Fig. 2. Occurrence of vascular complications in FH heterozygotes.

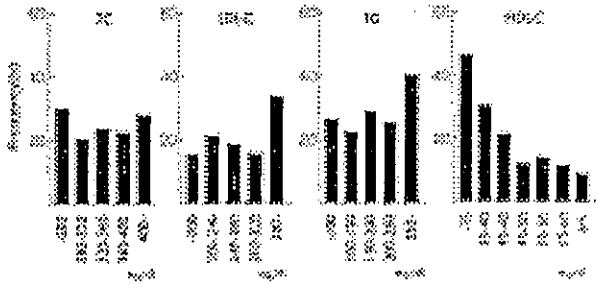

Fig. 1. Serum lipids and occurrence of CAD in FH homozygotes and heterozygotes.

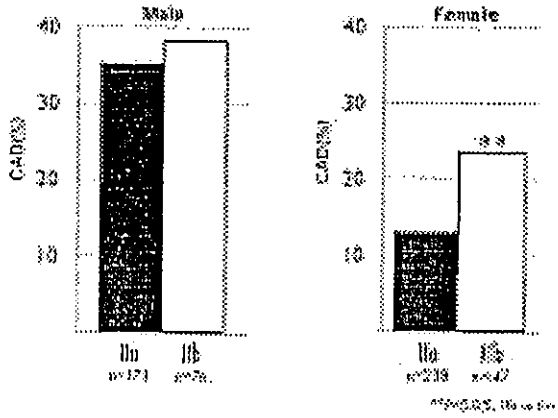

Fig. 3. Occurrence of CAD in the presence or absence of TG > 150 mg/dl in FH heterozygotes.

type IIa. Next, the significance of hypoalphalipoproteinemia (HDL-C of less than 40 mg/dl) was analyzed (Fig. 4). The cases with hypoalphalipoproteinemia showed increased CAD occurrence in males. Together with the results in Figure 1, serum HDL-C level seems to be rather well or related with CAD occurrence in FH heterozygotes.

Logistic regression analyses for CAD revealed that male, age > 50 y, smoking, hypertension, diabetes mellitus, TG > 150 mg/dl and HDL < 40 mg/dl were associated with an increased risk of CAD (Fig. 5). The cumulative incidence of CAD is shown in Fig. 6. Males with FH developed CAD 10-20 years earlier than females with FH.

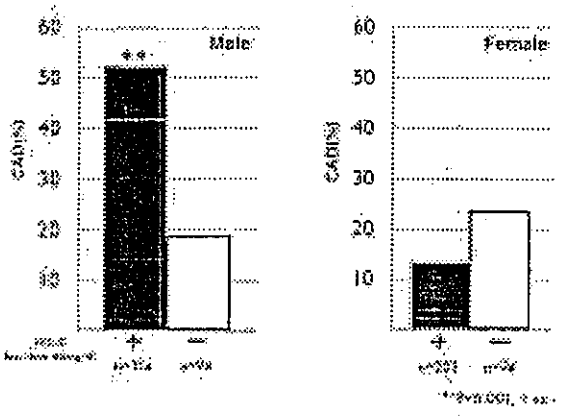

Fig. 4. Occurrence of CAD in the presence or absence of HDL-C < 40mg/dl in FH heterozygotes.

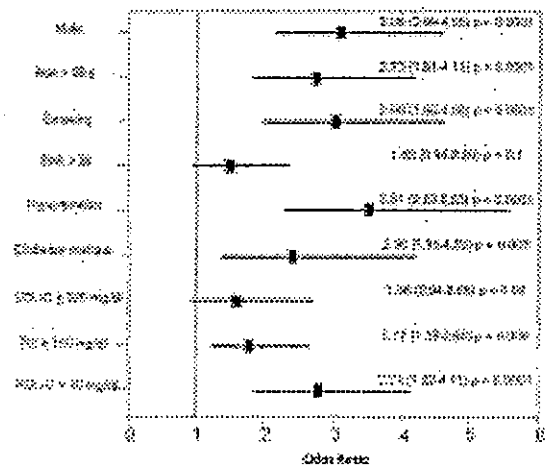

Fig. 5. Association between occurrence of CAD and conventional coronary risk factors in FH heterozygotes.

Phenotype of heterozygous cases with the "common mutations" in the LDL receptor gene

Common mutations in the LDL receptor gene have been suggested to exist in FH heterozygotes in Japan (6–8). The common mutations consist of four mutations: K790X in exon 17, C317S in exon 7 (FH Wakayama), P664L in exon 14 (FH Kanazawa-2) and 1845 + 2 T to C (FH Niigata). Previous studies have suggested that the total number of cases with the four mutations accounts for about 30% of heterozygous FH in Japan (6, 7). In order to determine the frequencies and clinical features of cases with the common mutations in various areas in Japan, the four mutations were intensively analyzed in the cases with FH in the Chiba area, and the frequencies and phenotypes were analyzed in comparison with previous data from other areas. The occurrences of the four mutations in the 154 cases of heterozygous FH in Chiba were observed as 5.8%, 4.5%, 5.2% and 1.9% for 1847TC, K790X, P664L and C317S, respectively (Table 3). The frequencies in Chiba were about one-half and one-third to-fourth for 1847TC and C317S, respectively, compared to those in the Osaka area. The frequencies of K790X and P664L were almost the same between both areas. The frequencies of P664L in both areas were also similar to that in the Kanazawa area. The frequency of cases with the four mutations was up to 17.5% of all FH cases analyzed in the Chiba area.

The clinical features of FH with the common mutations were analyzed next. The serum levels of both TC and LDL-C in the cases with the common mutations were increased compared to the average levels of the 641 cases with heterozygous FH (Table 4). The summarized data of the Chiba and Osaka areas (provided by Drs. Maruyama and Yamashita) showed that cases with any

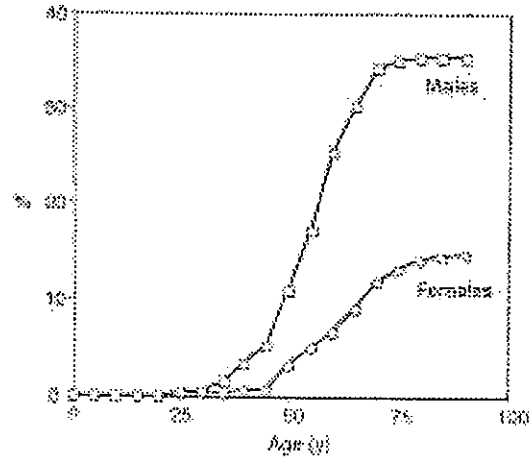

Fig. 6. Cumulative incidence of CAD in FH heterozygotes.

of the common mutations showed increased average TC and LDL-C levels compared to those in the data of heterozygous FH (Table 5). The frequencies of CAD occurrence were 52%, 54%, 36% and 54% for 1847TC, K790X, P664L and C317S, respectively. These occurrences in the cases with the common mutations were increased compared to those in the data of heterozygous FH, although the average age was younger in the cases with the common mutations. However, the average levels of TC and LDL-C of the cases with P664L (FH Kanazawa 2) in the Kanazawa area (provided by Drs. Kajinami and Mabuchi) were obviously decreased compared to the summarized levels (Table 6).

Discussion

The clinical features of FH in Japan were investigated using a database mutations in Japanese patients with primary hyperlipidemia and related disorders. Additionally, clinical phenotypes in FH with the common mutations were studied using three databases based on different areas in Japan. The clinical features and the frequencies of accompanying vascular diseases in 660 FH homozygotes and heterozygotes suggested that the occurrence of CAD has increased in males, and has not changed much in females, compared to that in the database from 1986, respectively (9). However, it is impossible to compare the occurrence exactly as the criteria for the definition of FH is not the same between the previous and current studies. There was no clear relationship between CAD occurrence and TC level in the annual report of the research group for primary hyperlipidemia in 1986, which is not clearly different from the results of this study. However, the annual report in 1986 showed a relationship between TG and CAD, which was not obviously observed in this study. The relationship

Table 3. Frequencies of common mutations in 3 areas in Japan.

Mutation	Chiba (n = 154)	Osaka (n = 120)	Kanazawa (n = 201)
1847TC	5.8% (9)	13.3% (16)	
K790X	4.5% (7)	6.7% (8)	
P664L (Kanazawa 2)	5.2% (8)	3.3% (4)	3.0% (6)
C317S	1.9% (3)	6.7% (8)	
Tonami 1			5.0% (10)
Tonami 2			5.5% (11)
Total	17.5% (27)	30.0% (36)	13.4% (27)

Table 4. Clinical features of FH heterozygotes with common mutations in the Chiba area.

Mutation	K790X	P664L	1847TC	C317S
n	7	8	9	3
Age (y)	50 ± 12	50 ± 17	50 ± 5	33 ± 20
Sex (M/F)	5/2	2/6	4/5	2/1
BMI (kg/m²)	23.2 ± 2.7	22.8 ± 2.7	21.3 ± 4.1	20.8 ± 1.6
TC (mg/dl)	406 ± 25	398 ± 73	384 ± 35	349 ± 70
LDL-C (mg/dl)	335 ± 40	323 ± 77	329 ± 43	292 ± 65
TG (mg/dl)	164 ± 86	146 ± 54	118 ± 57	133 ± 39
HDL-C (mg/dl)	38 ± 11	46 ± 13	44 ± 14	31 ± 4
ATT (max, mm)	14 ± 8	11 ± 5	19 ± 7	8 ± 1
Xanthoma (%)	20	17	25	0
CAD (%)	40	43	50	33

Mean ± SD, Xanthoma does not include Achilles tendon thickness.

Table 5. Clinical features of FH heterozygotes with common mutations in 3 areas (National Cardiovascular Center, Osaka University, Chiba University).

Mutation	K790X	P664L	1847TC	C317S
n	13	16	29	13
Age (y)	44 ± 14	43 ± 18	44 ± 14	41 ± 14
Sex (M/F)	6/7	4/12	12/17	7/6
BMI (kg/m²)	23.2 ± 1.7	22.7 ± 2.4	21.1 ± 2.9	22.2 ± 2.2
TC (mg/dl)	414 ± 90	377 ± 63	355 ± 74	381 ± 67
LDL-C (mg/dl)	346 ± 99	300 ± 64	282 ± 74	320 ± 63
TG (mg/dl)	149 ± 68	131 ± 55	140 ± 78	134 ± 55
HDL-C (mg/dl)	40 ± 12	51 ± 12	45 ± 14	34 ± 7
CAD (%)	54	36	52	54

Mean ± SD.

Table 6. Clinical features of FH heterozygotes with common mutations in the Kanazawa area.

Mutation	Kanazawa 2	Tonami 1	Tonami 2
n	15	22	34
Age (y)	40 ± 16	48 ± 19	52 ± 21
TC (mg/dl)	309 ± 45	338 ± 42	310 ± 69
LDL-C (mg/dl)	251 ± 43	272 ± 43	222 ± 61
TG (mg/dl)	126 ± 51	97 ± 41	158 ± 126
HDL-C (mg/dl)	35 ± 14	46 ± 12	40 ± 11

Mean ± SD.

observed between HDL-C and CAD was almost the same in both reports. The importance of accompanying hypertriglyceridemia in females and hypoalphalipoproteinemia in males for an increased occurrence of CAD was clarified in FH. Risk factor analyses revealed that hypertension, male, smoking, low HDL-cholesterol levels (< 40 mg/dl), age > 50 y, diabetes mellitus, and hypertriglyceridemia (> 150 mg/dl) were positive risk factors for coronary heart disease. The cumulative incidence of CAD showed that males with FH developed CAD 10–20 years earlier than females with FH.

A summarized gene analysis for hyperlipidemia showed at least four mutations in the LDL receptor gene as common mutations in Japan (6,7). The increased average serum lipids and frequencies of CAD suggested the differing phenotypic severity among FH cases based on various mutations. Further analysis of the clinical features of cases with the common mutations should be performed to determine the clinical severity in these cases.

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Current State of and Recent Trends in Serum Lipid Levels in the General Japanese Population

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Abstract

To determine the recent serum lipid levels and other serum variables in the general Japanese population and trends in their changes over the past 40 years, a nationwide survey of serum lipid levels was conducted in 36 institutes from various districts around Japan. The total number of subjects was 12,839 consisting of 7,658 men and 5,179 women aged 4 through 99 years. The mean total cholesterol level was 201 mg/dl; 202 mg/dl in men and 200 mg/dl in women. The mean HDL-cholesterol level was 59 mg/dl; 55 mg/dl in men and 65 mg/dl in women. The mean LDL-cholesterol level was 118 mg/dl; 121 mg/dl in men and 115 mg/dl in women. The mean triglyceride level was 118 mg/dl; 136 mg/dl in men and 92 mg/dl in women. The total cholesterol level was slightly increased by 5 mg/dl in 10 years. Although the triglyceride level in women was not changed, the triglyceride level in men was increased in 10 years, especially in the 30s through 70s, indicating a possible increase in the metabolic syndrome in the future. The present results will become the standard serum lipid level data for the Japanese people, and succeeding 10-year surveys will clarify the trends of lipid levels in this country.

Introduction

It has been well established that hyperlipidemia is a major risk factor for coronary heart disease (CHD) (1; 2). Numerous studies have shown that the reduction of serum lipid levels by dietary or drug treatment results in a decrease in both the incidence of and the mortality from CHD (3-7). In contrast to the sharp decline in both serum cholesterol and the mortality from CHD in the United States and Western Europe, remarkable increases in serum cholesterol levels as well as CHD mortality have been anticipated in the Asian-Pacific area due to industrialization and modernization of the lifestyle. Epidemiological studies indicate that changes in lifestyle have a great influence on the risk factors for atherosclerosis (8-10). Among the Asian-Pacific countries, Japan was found to have lower serum cholesterol values and a correspondingly lower incidence of CHD. Japanese in the 1960s consumed very little dietary fat, and both in cholesterol levels and the incidence of CHD were low. Japanese who migrated to Hawaii and California, however, showed higher levels of serum cholesterol and a higher incidence of CHD than people in Japan (10). Thus, dietary habits and other environmental factors rather than genetic background affect serum cholesterol levels and CHD mortality in the population. In the United States, during the period of 1900 through 1991, many changes in nutritional lifestyle and medical therapeutic factors may have decreased serum total cholesterol levels among American adults (11). On the other hand, Japanese have adopted mixed dietary habits of a traditionally low fat and low cholesterol diet and a western style diet of relatively high fat and high cholesterol. As a result the serum cholesterol levels in the Japanese populations were found to have gradually increased over the 30 years from 1960 to 1990 by the

10-year-interval national surveys of serum cholesterol levels conducted in 1960, 1970, 1980, and 1990 (12-14). This study is the fifth survey and reveals the most recent serum lipid levels as well as fasting glucose, hemoglobin A1c (HbA1c), insulin, and uric acid levels in the Japanese general population and the trends of serum lipid levels over the 40 years from 1960 to 2000.

Methods

Designs and Data Collection

The Research Group on Serum Lipid Level Survey 2000 in Japan organized the members of 36 institutes from various areas around Japan. The project was designed to produce representative data of serum lipid, , insulin, and uric acid plasma glucose and HbA1c levels in the civilian Japanese population. The subjects were people receiving annual health examinations in general community, companies, and schools, and not patient-visiting hospitals. The total number of subjects was 12,839, consisting of 7,658 men and 5,179 women. (Two of them were unknown for sex.)

Laboratory Methods

All serum and plasma samples were obtained in the fasting state except participants less than 20 years old, because it was hard to obtain permission of blood drawing in a fasting state in children. All lipid and other analyses were conducted on venous blood samples within one week of collection at BML (Saitama, Japan). Serum cholesterol and triglyceride levels were measured by enzymatic assay. HDL-cholesterol and LDL-cholesterol were measured enzymatically by a kit from Daiichi Kagaku Co. Ltd. (Tokyo, Japan). The results of lipid analyses in the four surveys were indirectly standardized according to the criteria of the CDC Lipid Standardization Program (11). There were

no differences between the data obtained by Zak-Henly's method in 1960 and 1970, and those by the enzymatic methods used in 1980 through 2000. Thus, the cholesterol levels in these five surreys appear to be comparable. In the present survey, we also measured remnant like particles (RLP)-cholesterol by a kit from Japan Immunoresearch Laboratories (Takasaki, Japan). Plasma glucose was determined enzymatically and HbA1c was determined by a kit from Kyowa Medics Co.Ltd (Tokyo, Japan). Serum insulin was determined by immunoradiometric assay (Abbott Diagnostics Division, Abbot Park, IL).

Data Analyses

The statistical analyses of the present data were performed by SAS statistical. The study was designed by the Research group, which organized 36 institutions from various districts of Japan from the extreme North (Hokkaido) to the furthest South (Okinawa) islands.

Results

Table 1 shows the age-specific means and standard deviations of serum total cholesterol levels by age group in all the participants as well as in men and women. The mean total cholesterol level in this survey was 201 mg/dl, which is 5 mg/dl higher than that in 1990. In men, the age-specific mean serum cholesterol levels gradually increased from 185 mg/dl in the 0- to 9-year-old age group to 207 mg/dl in the 50- to 59-year-old age group. There was a slight decrease after age 60. In women, the mean cholesterol levels gradually rose from 186 mg/dl in the 0- to 9-year-old age group to 218 mg/dl in the 50- to 69-year-old age groups, and fell to 208 mg/dl after age 80.

Table 2 shows the age-specific means and standard deviations of serum triglyceride levels in all the participants as well as in men and women. The mean triglyceride level in this survey was 118 mg/dl, which was 13 mg/dl higher than that in 1990. The age-specific mean triglyceride values in men increased from 53 mg/dl in the 0- to 9-year-old age group to 150 mg/ dl in the 40- to 49-year-old age group, followed by a decline to 88 mg/dl above 80 years old. In women, the age-specific mean triglyceride levels increased gradually from 59 mg/dl in the 0- to 9-year-old age group to 117 mg/dl in the 60- to 69-year-old age group, and then declined to 105 mg/dl above 80 years of age. Although the triglyceride level in women was not changed in ten years, the triglyceride level in men was markedly increased, especially 30- to 39-year-old to 70- to 79-year-old age group in the last ten years.

Table 3 shows the age-specific means and standard deviations in serum HDL-cholesterol levels in all the participants as well as in men and women. The mean HDL-cholesterol level in this survey was 59 mg/dl, which is 5 mg/dl higher than that in 1990. The age-specific mean HDL-cholesterol levels in men gradually decreased from 70 mg/dl in the 0-to 9-year-old age group to 54 mg/dl in the 30- to 39-year-old age group, and remained at this level up to 89 years old age. The mean HDL-cholesterol levels in woman remained constant from the 0- to 9-year-old age group to the 50- to 59-year-old age group, and gradually decreased thereafter.

Table 4 shows the age-specific means and standard deviations in serum LDL-cholesterol levels in all the participants as well as in men and women. LDL-cholesterol was measured directly, not by Friedewald equation. The mean LDL-cholesterol level in this survey was 118 mg/dl, which is

almost the same as that in 1990. The age-specific mean LDL-cholesterol levels in men gradually increased from 101 mg/dl in the 0- to 19-year-old age group to 125 mg/dl in the 50- 59-year-old age group. The age-specific mean LDL-cholesterol level in women increased from 93 mg/dl in the 20- to 29-year-old age group to 135 mg/dl in the 60- to 69-year-old age group, and then decreased slightly thereafter.

Table 5 shows the age-specific means and standard deviations in serum RLP-cholesterol levels in all the participants as well as in men and women. The mean RLP-cholesterol level in this survey was 4.5 mg/dl. The mean RLP-cholesterol level in men was significantly higher than that in women, and the tendency in age-specific means was similar to the triglyceride level. Fig. 1 summarizes the recent trend of the mean cholesterol level in young and middle-aged men and women from 1960 to 2000. The trend indicates a gradual increase in the total cholesterol level in men and women in almost all generations over the last 40 years in Japan.

Table 6 shows the age-specific means and standard deviations in plasma fasting glucose levels in all the participants as well as in men and women. The mean fasting glucose level in this survey was 95 mg/dl. The mean glucose level was slightly higher in men than in women. The glucose level had a tendency gradually increasing according to age in both men and women. HbA1c levels also had a tendency gradually increasing according to age in both men and women. However, the mean HbA1c levels in men and women were almost the same in each age group (Table 7). We also measured the serum insulin level in this survey. The serum insulin level was almost constant except in the 20- to 29-year-old age group and the mean insulin level in this survey was 7 μU/ml

(Table 8).

Finally, we determined uric acid levels. The mean uric acid level in this survey was 5.4 mg/dl. The mean uric acid level was significantly higher in men than in women. Although the level of uric acid in men was almost constant in all age groups, the uric acid level in women was gradually increased according to age.

Discussion

In this survey we found that the mean total cholesterol level in Japanese general population increased by 5 mg/dl in the last 10 years. This increase, however, is attributed to the increase in HDL-cholesterol, but not to LDL-cholesterol. The triglyceride level is also increased in the last 10 years. This increase is attributed to the increase in middle-aged men, making us anticipate a further increase in the incidence of hypertriglyceridemia in the future. The significance of triglyceride as a risk factor for CHD has recently obtained more attention world-wide, and its relationship with hyperinsulinemia and glucose intolerance is emphasized (15; 16). In the analysis by Yamamoto et al on the survey in 1990, they concluded that the most important cause of hypertriglyceridemia would be overweight. According to the survey conducted by the Ministry of Health, Labor, and Welfare the body mass index is increasing from 1980 to 2000 only in men. Therefore, as clinicians we need to encourage life style changes, such as more exercise and Japanese food instead of western diet to the Japanese general population, especially men. Unless we can change our life style in Japan, more people will die from cardiovascular disease in the 21st century.

Guidelines for the proper management of risk factors, targeting the prevention and treatment of atherosclerotic disease, have been established in the United States (17; 18) and Europe (19). The Japan Atherosclerosis Society also published a guideline for the management of hyperlipidemia for the prevention of CHD in 2002. As the American and European guidelines, the Japanese guideline also emphasized the importance of the management of high risk patients, such as patients with multiple risk factors or diabetes as well as those with established CHD. Although our survey shows no increase in LDL-cholesterol level, the triglyceride level was significantly increased in the last 10 years. Especially, the male mean triglyceride level in their 40s is 150 mg/dl, indicating about half of the participants have hypertriglyceridemia. Because hypertriglyceridemia is one of the criteria of the metabolic syndrome, our result implies that the number of the patients with the metabolic syndrome will increase in Japan. Therefore, in the next survey in 2010, we will investigate the incidence of the metabolic syndrome in Japanese general population after establishing a guideline of the metabolic syndrome for Japanese. This survey also indicates that we as the members of the Japan Atherosclerosis Society have to make every effort to call more clinical attention for the management of dyslipidemia for the prevention of CHD.

Currently approximately 4 million people are taking statins for hyperlipidemia in Japan. In this survey about 5% of the participants were turned out to take lipid-lowering drug, most of which are supposed to be statins. The mean total cholesterol level of the participants without lipid lowering drugs was 209 mg/dl, which is slightly higher than the mean total cholesterol levels of all the participants. In this sense, the participants in this survey represent the general population in

Japan. Use of lipid-lowering drugs, such as statins would be more important for the treatment of high risk patients to prevent CHD.

In 2000, another survey was done at the same time, conducted by the Ministry of Health, Labor, and Welfare. In this study, more subjects were selected from rural, agricultural, and mountain areas, and there was no rise in serum cholesterol in the last 10 years (from 1990 to 2000). In this study carried out by the members of the Japan Atherosclerosis Society more subjects from urban areas were included. In both studies, the cholesterol levels used to be significantly lower in the districts including wider agricultural and mountain areas than in the districts including large cities like Tokyo and Osaka in 1980. In 1990, the difference in serum cholesterol levels was no longer significant between urban, rural, and mountain village areas. Therefore, it is not clear why these studies show a different trend in the cholesterol level.

In this survey we also determined fasting glucose, insulin, and HbA1c levels of approximately 10,000 participants. We think that this is the largest survey for glucose metabolism in Japan. Our data indicate that the glucose and HbA1c levels are gradually increasing according to age in both sexes. However, the plasma insulin levels are almost constant in all age groups. We also showed that the uric acid level is significantly higher in men than in women. This is consistent with the data that the incidence of hyperuricemia and gout is higher in males than in females. Alcohol consumption would contribute to the higher level of uric acid in men. According to the database from the Ministry of Health, Labor, and Welfare (http://www.mhlw.go.jp/toukei/), the incidence of hyperuricemia in men and women is increasing in Japan. Because hyperuricemia is related to

obesity, hypertension, and insulin resistance, and eventually to the incidence of CHD, controlling the uric acid level would be important for the prevention of CHD in Japan.

Thus this report tells us the importance of the prevention and treatment of hyperlipidemia for the prevention of CHD in Japan. We need to establish a guideline for the life style change to prevent the further increase of dyslipidemia in the future.

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Appendix

Research Group on Serum Lipid Survey 2000 in Japan

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