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III. 研究成果の 刊行物・別冊

Serum Lipid Survey and Its Recent Trend in the General Japanese Population in 2000

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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 in 2000. The total number of subjects was 12,839, 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 slightly increased by 5 mg/dl in 10 years. Although the triglyceride level in women did not change, the triglyceride level in men increased over 10 years, especially in the 30s through 70s age bracket, indicating a possible increase in metabolic syndromes 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. *J Atheroscler Thromb*, 2005; 12: 98-106.

Key words: Hyperlipidemia, Cholesterol, Triglyceride, Life style, Coronary heart disease

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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 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 region, due to industrialization and modernization. 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 than average serum cholesterol values and a correspondingly lower incidence of CHD. Japanese in the 1960s consumed very little dietary fat, and both 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 according to 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 general Japanese population, and the trends of serum lipid levels over the 40 years from 1960 to 2000.

Methods

Designs and data collection

The Research Group for Serum Lipid Level Survey 2000 in Japan co-ordinated members of 36 institutes from various areas in 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 the general community, companies, and schools, and not patients 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, be-

cause it was hard to obtain permission to sample blood from children in a fasting state. 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 Daichi 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 surveys appear to be comparable. In the present survey, we also measured remnant-like particles (RLP)-cholesterol with a kit from Japan Immunoresearch Laboratories (Gunma, Japan). Plasma glucose was determined enzymatically and HbA1c was determined using a kit from Kyowa Medex Co. Ltd (Tokyo, Japan). Serum insulin was determined by immunoradiometric assay (Abbott Laboratories, Abbot Park, IL, USA).

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 were highest in 30- to 49-year-old age group in men. In contrast, 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 did not change in ten years, the triglyceride level in men has markedly increased, especially 30- to 39-year-old to 70- to 79-year-old age groups over 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

Table 1. List of the institutes enrolled for this survey from each district around Japan.

Area	Name of Institute
Hokkaido	Sapporo Medical University
	Hokkaido University
	Asahikawa Red Cross Hospital
Tohoku	Yamagata University
	Hirosaki University
	Mizusawa General Hospital
Kantou	Tsukuba University
	Teikyo University
	St. Luka's International Hospital
	Chiba University
	National Defense Medical College
	Tokyo University
	Toranomon Hospital
	Nihon Medical School
	Nihon University
	Hokuriku/Tokai
Kanazawa University	
University of Fukui Faculty of Medical Sciences	
Himi Municipal Hospital	
Nagoya University	
Sugiyama Jogakuen University	
Kinki	National Cardiovascular Center
	Osaka University
	Kyoto Center for Preventive Medicine
	Kobe University
Chugoku/Shikoku	Egusa Clinic
	Yamaguchi University
	Chugoku Central Hospital
	Udajima Social Insurance Hospital
Kyushu/Okinawa	National Hospital Organization
	Kumamoto Medical Center
	Fukuoka University
	Saga University Faculty of Medicine
	Kagosima University
	Miyazaki Prefectural Nichinan Hospital
	University of Ryukyus

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. Figure 1 summarizes the

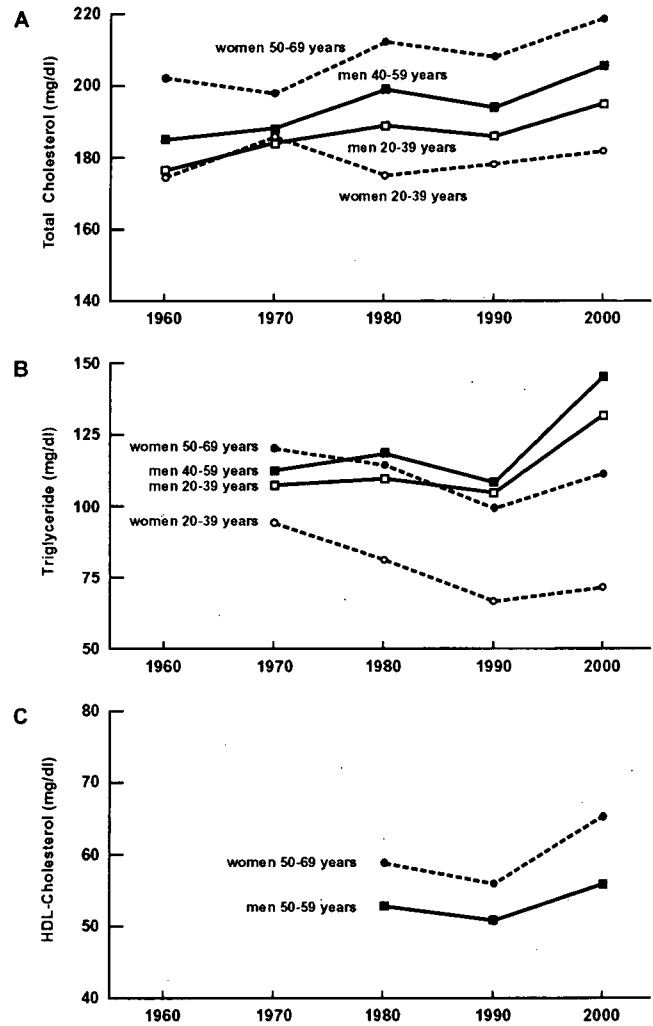


Fig. 1. Trends of serum lipid levels in Japanese in 40 years from 1960 to 2000. Results of the surveys carried out by the members of Japan Atherosclerosis Society. A. The mean cholesterol level in men and women of 20–39 years, men of 40–59 years, and women of 50–69 years from 1960 to 2000. B. The mean triglyceride level in men and women of 20–39 years, men of 40–59 years, and women of 50–69 years from 1970 to 2000. C. The mean HDL-cholesterol level in men and women of 50–59 years from 1980 to 2000.

Table 2. Serum total cholesterol (mg/dl) for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	216	186	27	102	185	26	114	186	27
10-19	465	181	28	196	178	28	269	183	27
20-29	1,256	180	31	394	181	32	861	180	31
30-39	1,642	195	34	1,101	200	34	541	185	31
40-49	3,564	201	33	2,399	204	32	1,165	195	32
50-59	3,467	211	34	2,328	207	33	1,139	218	34
60-69	1,625	209	34	844	200	34	780	218	32
70-79	551	206	33	271	198	32	280	214	32
80-89	53	197	33	23	181	29	30	208	32
Total	12,839	201	34	7,658	202	34	5,179	200	35

Table 3. Serum triglyceride (mg/dl) for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	216	56	30	102	53	30	114	59	30
10-19	465	67	36	196	66	39	269	68	33
20-29	1,256	83	65	394	105	74	861	73	58
30-39	1,642	118	109	1,101	142	123	541	70	42
40-49	3,564	129	103	2,399	150	112	1,165	87	63
50-59	3,467	129	102	2,328	139	115	1,139	108	66
60-69	1,625	123	83	844	128	98	780	117	64
70-79	551	118	63	271	123	67	280	113	59
80-89	53	100	44	23	93	38	30	105	47
Total	12,839	118	96	7,658	136	109	5,179	92	62

recent trend of the mean total cholesterol, triglyceride, and HDL-cholesterol levels 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. The trend of the triglyceride level was somewhat different from that of the total cholesterol level. The triglyceride level in women, especially in young women, has tended to decrease over the last 30 years, while the level in men dramatically has increased in the last 10 years. The level of HDL-cholesterol increased both in men and women in the last 10 years.

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- to 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.

In this survey we also measured RLP-cholesterol levels to assess the level of remnant particles. 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 age-specific mean RLP-cholesterol values were highest in 30- to 49-year-old age group in men as found in the triglyceride levels. The trends in age-specific means were similar to those of the triglyceride level. As expected, the RLP-cholesterol level correlated with the triglyceride level. (data not shown, $R = 0.878$, $p < 0.0001$).

Table 6 shows the age-specific means and standard deviations in plasma fasting glucose levels in all the par-

ticipants 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 to gradually increase

according to age in both men and women. HbA1c levels also had a tendency to gradually increase according to age in both men and women. However, the mean HbA1c levels in men and women were almost the same in each

Table 4. Serum HDL-cholesterol (mg/dl) for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	216	69	15	102	70	15	114	68	16
10-19	465	65	14	196	63	14	269	66	13
20-29	1,255	64	14	393	56	13	861	68	14
30-39	1,637	58	15	1,096	54	14	541	67	14
40-49	3,545	58	15	2,380	55	14	1,165	65	15
50-59	3,434	59	16	2,295	56	15	1,139	65	16
60-69	1,614	57	14	833	55	14	780	60	14
70-79	551	57	15	271	55	15	280	60	15
80-89	53	58	16	23	54	12	30	61	18
Total	12,770	59	15	7,589	55	14	5,179	65	15

Table 5. Serum LDL-cholesterol (mg/dl) for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	154	104	22	70	101	22	84	106	22
10-19	162	103	24	51	101	21	111	104	25
20-29	713	97	24	240	105	26	472	93	22
30-39	751	112	29	484	119	29	267	101	25
40-49	1,179	121	30	750	124	31	429	116	29
50-59	1,243	127	30	733	125	30	510	130	30
60-69	726	129	31	387	124	30	338	135	29
70-79	246	126	28	117	120	27	129	130	28
80-89	32	123	29	10	113	27	22	127	30
Total	5,206	118	31	2,842	121	30	2,362	115	31

Table 6. Serum RLP-cholesterol (mg/dl) for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	265	1.9	0.6	70	2.0	0.6	84	1.9	0.7
10-19	161	2.5	1.2	51	2.5	1.1	110	2.5	1.3
20-29	712	3.5	3.1	240	4.5	4.2	471	2.9	2.2
30-39	762	5.0	6.0	493	6.2	6.9	269	2.7	2.6
40-49	1,211	5.2	7.7	774	6.2	8.7	437	3.2	4.9
50-59	1,322	4.8	6.2	791	5.2	7.4	531	4.3	3.7
60-69	662	4.6	7.3	363	5.1	9.4	298	4.1	3.5
70-79	206	4.1	3.7	98	4.3	4.4	108	4.0	2.9
80-89	28	3.7	2.5	8	2.4	1.6	20	4.2	2.7
Total	5,218	4.5	6.2	2,888	5.4	7.6	2,328	3.4	3.5

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 7.3 μ U/ml (Table 8). The mean insulin level was slightly higher in

women than in men.

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 (Table 9). Although the level of uric acid in men was al-

Table 7. Fasting glucose (mg/dl) for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	158	88	7	74	88	7	84	87	6
10-19	170	85	6	57	87	7	113	85	6
20-29	996	88	16	340	89	20	655	87	13
30-39	1,281	92	15	886	93	14	395	90	18
40-49	2,865	95	18	2,018	97	19	847	90	12
50-59	2,909	99	20	2,002	101	20	907	94	19
60-69	1,489	98	21	752	102	25	737	95	15
70-79	531	98	16	257	99	16	274	97	15
80-89	52	103	27	22	104	36	30	102	20
Total	10,451	95	19	6,408	98	20	4,042	92	16

Table 8. HbA1c for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	155	4.7	0.2	72	4.7	0.2	83	4.7	0.2
10-19	171	4.7	0.3	58	4.7	0.3	113	4.6	0.3
20-29	1,147	4.6	0.4	374	4.6	0.6	772	4.6	0.3
30-39	1,261	4.7	0.5	871	4.7	0.5	390	4.7	0.4
40-49	2,536	4.9	0.6	1,844	4.9	0.7	692	4.8	0.5
50-59	2,676	5.1	0.7	1,879	5.1	0.7	797	5.1	0.7
60-69	1,141	5.2	0.8	614	5.3	0.9	527	5.2	0.6
70-79	443	5.3	0.7	209	5.3	0.7	234	5.4	0.8
80-89	52	5.4	0.8	22	5.4	1.0	30	5.3	0.6
Total	9,582	4.9	0.7	5,943	5.0	0.7	3,638	4.9	0.6

Table 9. Serum insulin (μ U/ml) for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	216	6.7	5.2	102	6.5	6.2	114	6.9	4.1
10-19	463	7.1	7.2	196	6.1	5.1	267	7.9	8.3
20-29	1,171	11.4	12.9	382	9.9	10.6	788	12.1	13.8
30-39	1,410	8.2	9.0	942	8.3	8.9	468	8.0	9.2
40-49	2,734	6.7	5.5	1,877	6.7	5.0	857	6.6	6.4
50-59	2,636	6.4	5.6	1,731	6.0	4.2	905	7.3	7.5
60-69	1,118	6.1	5.3	589	5.9	5.3	528	6.4	5.2
70-79	440	6.2	14.8	211	5.2	5.6	229	7.1	19.7
80-89	53	5.8	4.6	23	6.1	5.8	30	5.6	3.6
Total	10,241	7.3	8.0	6,053	6.8	6.2	4,186	8.0	10.0

most constant in all age groups, the uric acid level in women gradually increased according to age (Table 10).

Discussion

In this survey we found that the mean total cholesterol level in the 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 has 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 is overweight. According to the survey conducted by the Ministry of Health, Labor and Welfare, the body mass index increased from 1980 to 2000 only in men, but not women. Therefore, the increase in triglyceride levels in Japanese men correlates with the increase of obese men. RLP-cholesterol is implicated as an atherogenic lipoprotein and our data showed a correlation of RLP-cholesterol with the triglyceride level. Therefore, we also should pay attention to the level of RLP-cholesterol. The importance of RLP-cholesterol in the prevention of CHD, such as being a marker for postprandial hyperlipidemia, should be determined in a future trial. Thus to reduce the triglyceride levels, we need to encourage lifestyle changes, such as more exercise and consuming a traditional Japanese diet instead of a modern 'western' diet in the Japanese general population, especially amongst men. Unless we can change our lifestyle in Japan, more people will die from cardiovascular disease in the 21st century.

In spite of the dramatic increase in the triglyceride level in men in the last 10 years, the HDL-cholesterol level also increased in the last 10 years. This is a somewhat unexpected finding, because hypertriglyceridemia is generally associated with a decrease in the HDL-cholesterol level. In this survey we changed the method of measuring HDL-cholesterol from the precipitation method to the enzymatic method. However, we have confirmed that this change of method does not affect the level of HDL-cholesterol. Therefore, we have at the moment no idea why both triglyceride and HDL-cholesterol increased in the last 10 years only in men.

Guidelines for the proper management of risk factors, and for 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 in 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 (20). Although our survey shows no increase in LDL-cholesterol level, the triglyceride level was significantly increased in the last 10 years. Especially, the mean triglyceride level of men in their 40s is 150 mg/dl, indicating about half of the participants have hypertriglyceridemia. Because hypertriglyceridemia is one criteria of metabolic syndrome, our result implies that the number of the patients with metabolic syndrome will increase in Japan. Therefore, in the next survey in 2010, we will investigate the incidence of the metabolic syndrome in the general Japanese population after establishing guidelines for the management of metabolic syndrome in Japan. This survey also indicates that we, as the members of the Japan Atherosclerosis Society, have to make every effort to call more clinical attention to the

Table 10. Serum uric acid (mg/dl) for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	0	-	-	0	-	-	0	-	-
10-19	3	6.7	0.7	3	6.7	0.7	0	-	-
20-29	410	4.7	1.4	137	6.1	1.3	273	4.0	0.8
30-39	927	5.6	1.5	714	6.0	1.3	213	4.0	0.9
40-49	2,425	5.5	1.5	1,763	6.1	1.3	662	4.1	0.9
50-59	2,459	5.5	1.4	1,762	6.0	1.3	697	4.3	0.9
60-69	1,141	5.2	1.4	618	5.8	1.3	523	4.5	1.0
70-79	296	5.1	1.5	152	5.8	1.4	144	4.4	1.1
80-89	25	4.9	1.6	8	5.0	0.9	17	4.9	1.8
Total	7,686	5.4	1.4	5,157	6.0	1.3	2,529	4.3	1.0

management of dyslipidemia for prevention of CHD.

Currently approximately 4 million people are taking statins for hyperlipidemia in Japan. In this survey about 5% of the participants were taking lipid-lowering drugs, 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 conducted by the Ministry of Health, Labor, and Welfare. In this study, more subjects were selected from rural, agricultural, and mountainous areas, and the results showed 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 were significantly lower in the agricultural and mountainous districts 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. However, Kuzuya et al also found an increase in total cholesterol levels from 1989 to 1998 in Aichi Prefecture in the central region of Japan (21).

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 of glucose metabolism in Japan. Our data indicate that the glucose and HbA1c levels gradually increased 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 was 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 guidelines for lifestyle change to prevent the further increase of dyslipidemia in the future.

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Appendix

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Serum Soluble Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 Levels Are Elevated in Acute Coronary Syndrome

A Novel Marker for Early Diagnosis

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Background—Markers of cardiac injury, including troponin-T (TnT), are used to diagnose acute coronary syndrome (ACS); however, markers for plaque instability may be more useful for diagnosing ACS at the earliest stage. Lectin-like oxidized LDL receptor-1 (LOX-1) appears to play crucial roles in the pathogenesis of atherosclerotic plaque rupture and ACS onset. LOX-1 is released in part as soluble LOX-1 (sLOX-1) by proteolytic cleavage.

Methods and Results—We examined serum sLOX-1 levels in 521 patients, consisting of 427 consecutive patients undergoing coronary angiography, including 80 ACS patients, 173 symptomatic coronary heart disease patients, 122 patients with significant coronary stenosis without ischemia, and 52 patients without apparent coronary atherosclerosis plus 34 patients with noncardiac acute illness and 60 patients with noncardiac chronic illness. Time-dependent changes in sLOX-1 and TnT levels were analyzed in an additional 40 ACS patients. Serum sLOX-1 levels were significantly higher in ACS than the other groups and were associated with ACS as shown by multivariable logistic regression analyses. Given a cutoff value of 1.0 ng/mL, sLOX-1 can discriminate ACS from other groups with 81% and 75% of sensitivity and specificity, respectively. sLOX-1 can also discriminate ACS without ST elevation or abnormal Q waves and ACS without TnT elevation from non-ACS with 91% and 83% of sensitivity, respectively. Peak values of sLOX-1 in ACS were observed earlier than those of TnT.

Conclusions—sLOX-1 appears to be a useful marker for early diagnosis of ACS. (*Circulation*. 2005;112:812-818.)

Key Words: angina ■ atherosclerosis ■ lipoproteins ■ myocardial infarction ■ receptors

Acute coronary syndrome (ACS) is one of the major causes of mortality and morbidity in developed countries. Accurate diagnosis of ACS at the earliest stage would improve prognosis through appropriate treatment without delay. ACS appears to be provoked by a rupture of lipid-rich atheromatous plaques, followed by thrombus formation.^{1,2} Several diagnostic tests such as echocardiography,³ radioisotope scintigraphy,⁴ and measurement of circulating levels of troponin-T (TnT)^{5,6} and the MB isoform of creatine kinase (CPK)⁷ have been used to detect ischemic myocardial damage in clinical practice; however, none of these markers directly indicates plaque instability or rupture before myocardial damage becomes apparent. Such markers for plaque instability or rupture would establish the diagnosis of ACS at

the earliest stage and may predict the onset. Several serum markers, including high-sensitivity C-reactive protein (hs-CRP),⁸ oxidized LDL (Ox-LDL),⁹ and soluble forms of membrane proteins such as CD40 ligand (CD40L),^{10,11} ICAM-1,^{12,13} and E-selectin,^{12,13} were reported to be associated with ACS or acute myocardial infarction. Although soluble CD40L has recently been shown to be correlated with prognosis after ACS,¹⁴ none of these markers has been established as a diagnostic marker of ACS at the earliest stage.

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LDL-lowering therapy has been shown to decrease the incidence of ACS and other atherosclerosis-related diseases.

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